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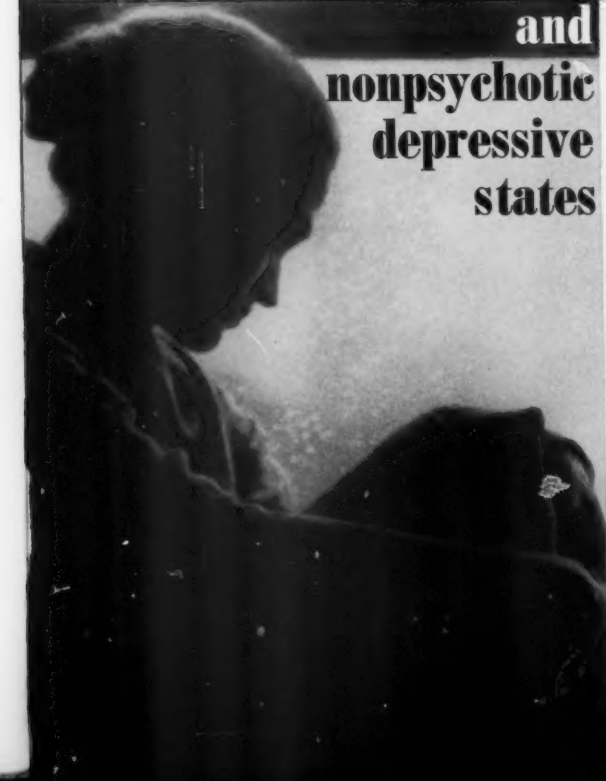

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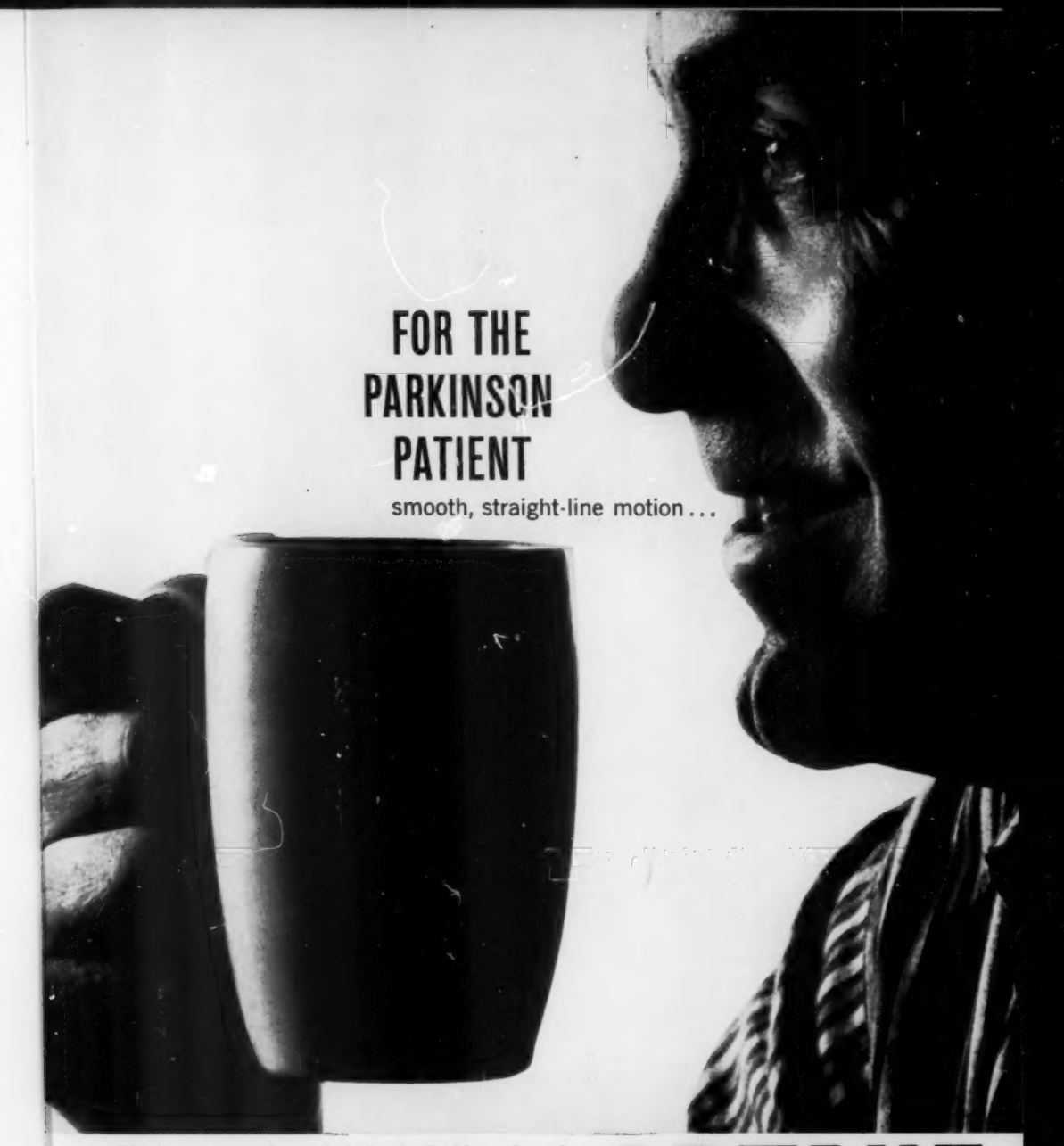

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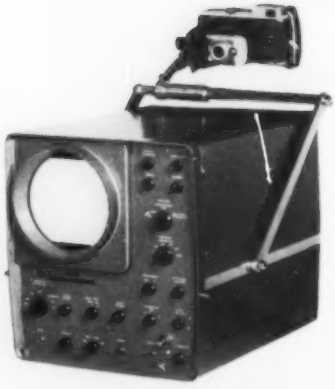

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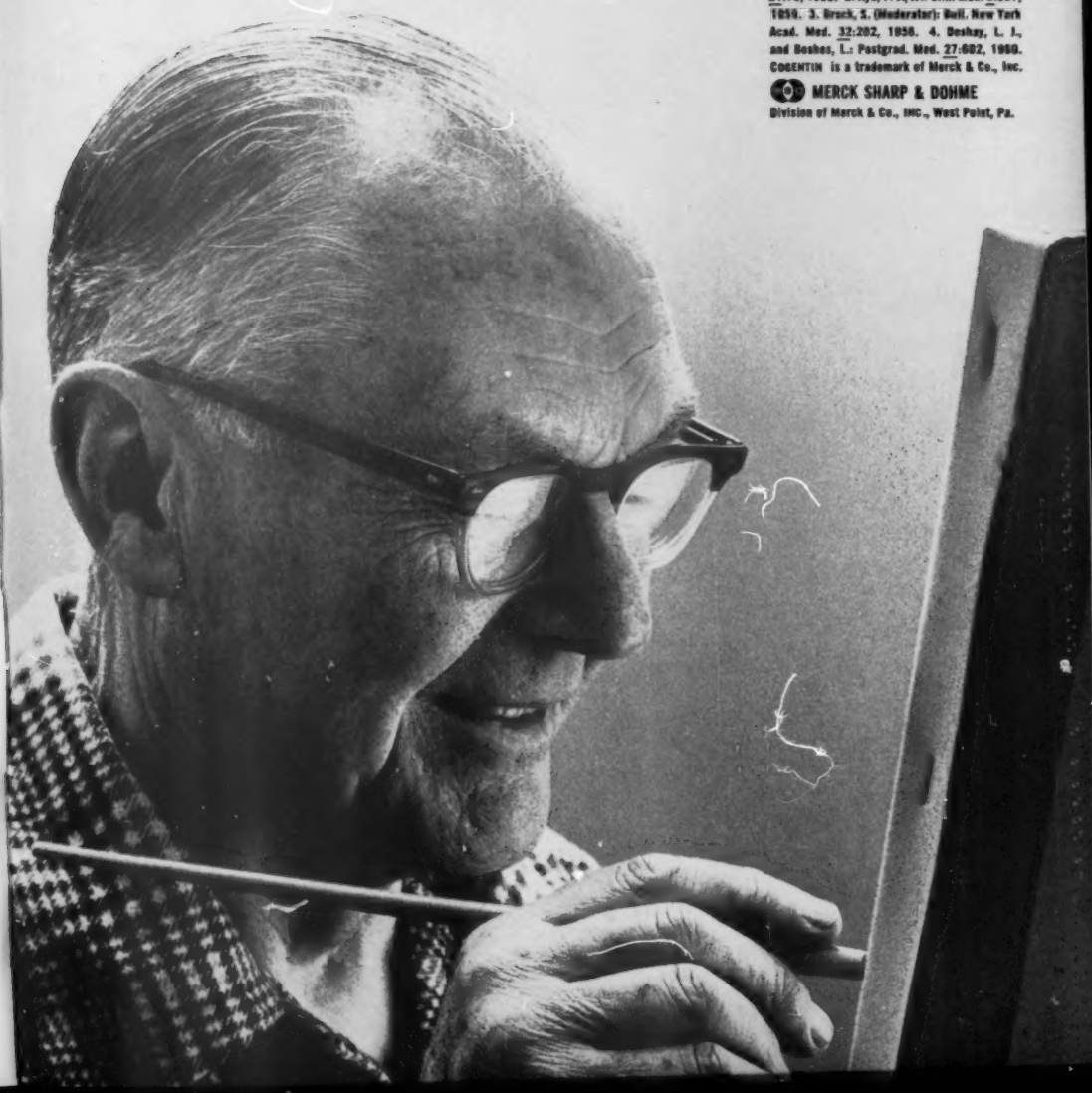

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Neurology Volume 11 • Number 4

The neuropathies associated with diabetes mellitus

A clinical and electromyographic study of 103 unselected diabetic patients

Donald W. Mulder, M.D., Edward H. Lambert, M.D., James A. Bastron, M.D., and Randall G. Sprague, M.D.

THE ASSOCIATION of neuropathy and diabetes has been recognized for many years. In the routine course of our clinical practice, we have seen many diabetic patients who were selected for referral to the neurologist because of severe neurologic problems. In the past, electromyographic studies, including measurements of the excitability and conduction velocity of the motor fibers of peripheral nerves, have given us objective and reproducible information about the function of peripheral nerves with diabetic neuropathies as well as with other diseases of the peripheral nerves.

The frequency of occurrence of neuropathy in diabetic patients is disputed. In an attempt to obtain a better definition of the frequency, clinical manifestations, and clinical course of diabetic neuropathy, we have studied occurrence of this complication in a relatively unselected group of diabetic patients, the great majority of whom would not have been referred for neurologic evaluation in our ordinary clinical practice. Such clinical studies of neuropathy in unselected diabetic patients have been reported in the past. In the present study, the problem has been reinvestigated with the independent use of the clinical examination and electromyographic technics to determine whether signs of neuropathy were present.

METHOD

Included in this study were 103 ambulatory patients for whom the diagnosis of diabetes mellitus had been made by our colleagues in metabolism. These were patients seen in the outpatient diabetic service who were available for electromyographic and neurologic examinations during the course of this study. By

From the Sections of Neurology, Physiology, and Medicine, Mayo Clinic and Foundation, Rochester, Minn.

This investigation was supported in part by Research Grant B-1592 from the U. S. Public Health Service.

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chance, the group did not include any patient who had peripheral neuropathy as a major difficulty.

Neurologic evaluations were carried out by two of us (Mulder and Bastron). A neurologic history was taken from, and a neurologic examination was conducted for, each patient. Only when there was objective evidence of reflex change, sensory abnormality, or muscle weakness was the clinical diagnosis of neuropathy made. In addition to the neurologic and routine medical evaluations, all these patients underwent funduscopic examinations by an ophthalmologist.

Neurophysiologic studies were carried out independently in the electromyographic laboratory (Lambert).[1] Studies of conduction in motor fibers of the ulnar, median, and peroneal nerves were carried out in each patient. The action potential evoked in the hypothenar, thenar, and extensor digitorum brevis muscles, respectively, by a single maximal electric stimulus applied to the nerve was detected by electrodes on the surface of the skin and recorded on a cathode-ray oscilloscope. Measurements were made of the latency, amplitude, and duration of the muscle response. Conduction velocity of the motor fibers of the nerves was estimated on the basis of the difference in latency of the muscle response after stimulation of the nerve at two points along its length, for example, at the elbow and wrist. In addition to the studies of nerve conduction, a conventional electromyographic examination with use of a needle electrode to detect the electric activity of muscle at rest and during voluntary contraction was carried out among 80 of the patients. Usually, small muscles of the hands and feet and the gastrocnemius and anterior tibial muscles were examined in this way. In most instances, the muscles and nerves were examined on one side of the body only. In some instances, many more muscles and nerves were examined.

The electromyographic findings were regarded as abnormal when fibrillation potentials or a marked reduction of the number of motor action potentials, or both, were observed. Results of studies of nerve conduction were reported as abnormal in the case of a specific nerve when the amplitude of the action potential evoked in the appropriate muscle was less than 5.6 mv. with maximal stimulation of the ulnar nerve, 5 mv. on stimulation of the median nerve, and 2 mv. after stimulation of the peroneal nerve. The latency of the response was judged abnormal when the interval between stimulation of the ulnar nerve at the wrist and the response of the hypothenar muscle was more than 4 msec. Latency of response of the median nerve was judged to be abnormal when the interval was greater than 4.7 msec. and in the case of the peroneal nerve, more than 7 msec. Conduction velocity of the nerve (between elbow and wrist or knee and ankle) was considered abnormal when it decreased to less than 47 meters per second in the ulnar nerve, 45 meters per second in the median nerve, and 40 meters per second in the peroneal nerve. A diagnosis of neuropathy was made when two or more of these measurements were abnormal.

OBSERVATIONS

At the time of examination, the patients' ages varied from 11 to 79 years. Duration of the diabetes varied from that of newly discovered disease to thirty-seven years. Severity and adequacy of control (Table 1) of the diabetes were similarly varied. In addition to the diabetes and associated neuropathy, other diseases were recognized in these patients. The following diagnoses were made in individual patients: multiple sclerosis, familial or essential tremor, syndrome of protruded intervertebral disk in the lumbar area, hemiplegia apparently secondary to a cerebral infarct, syphilis, myxedema, and hyperthyroidism. Evidence of arteriosclerosis with incompetence of blood flow in coronary or peripheral vessels was observed in 29 patients. Diabetic retinopathy[2] was present in 27 patients, and 2 patients had the Kimmelstiel-Wilson syndrome.

Using the neurologic and electromyographic criteria described earlier in this paper, we found that 47 of the patients in this study did not have neuropathy (Table 1). In 2 of these patients, both more than 70 years old, the gastrocnemius reflexes were diminished but not absent. These findings were not interpreted as abnormal. In 31 of the 103 patients, there were sufficient clinical or electromyo-

TABLE 1
CLINICAL DATA: 103 PATIENTS WITH DIABETES MELLITUS OF WHOM 43 HAD NEUROPATHY

Age, years, inclusive	*No neuritis*	*Mononeuropathy*		*Polyneuropathy*		*Patients, total*
		Equivocal	*Certain*	*Equivocal*	*Certain*	
Through 19	2	1	1			4
20-29	1			1		2
30-39	4		1		2	7
40-49	12	1			4	17
50-59	13	1	3	1	10	28
60-69	9	1	5	6	12	33
70-79	6		2	1	3	12
Totals	47	4	12	9	31	103
Sex						
M	30	3	7	5	18	63
F	17	1	5	4	13	40
Totals	47	4	12	9	31	103
Duration, years, inclusive						
New	13		4	3	4	24
Through 1	7	1			2	10
2-5	9	1	3	3	2	18
6-10	4	2		2	8	16
11-20	12		5	1	10	28
20+	2				5	7
Totals	47	4	12	9	31	103
*Grade**						
1	7		1	1	2	11
2	9	1	2	1	2	15
3	16	2	5	4	11	38
4	15	1	4	3	16	39
Totals	47	4	12	9	31	103
Peripheral or coronary arteriosclerosis	11	1	4	4	9	29
Retinopathy	6		2	3	16	27
Totals	17	1	6	7	25	56

*Grade 1 diabetes is controlled by restriction of intake of concentrated carbohydrates alone.
Grade 2 diabetes is controlled by limitation of intake of carbohydrates to approximately 150 gm. daily.
Grade 3 diabetes requires diet control plus insulin, up to 30 units daily, or diet plus an oral hypoglycemic agent.
Grade 4 diabetes requires diet control plus insulin, 30 or more units daily.

graphic data to warrant a positive diagnosis of diffuse peripheral neuropathy. The clinical syndrome in these patients was characterized by pain, tenderness, and hypesthesia in the lower extremities in the more severe forms of the illness, and, in all these patients, it was associated with diminished to absent Achilles reflexes and impaired sense of vibration at the ankles. In an additional 9 patients, the clinical and electromyographic evidence was equivocal and suggested polyneuropathy; however, a positive diagnosis could not be made.

In 12 patients, evidence of selective involvement of one or more nerves was considered to represent mononeuropathy—that is, these patients had involvement of the motor and sensory components of only 1 or 2 peripheral nerves. In addition, evidence of mononeurop-

athy was present in 4 patients who also had evidence of polyneuropathy. These patients already have been included in the group of the 31 patients with polyneuropathy.

In the total group of 16 patients with mononeuropathy, 29 nerves were selectively involved. The common peroneal nerve was involved in 13 patients in whom the symptoms and findings seemed similar to those of the commonly described crossed-leg palsy. In 9 patients, clinical findings were limited to the distribution of the median nerve, with evidence on nerve-stimulation studies of impaired conduction of this nerve as it passed through the carpal tunnel at the wrist. Symptoms and findings of a tardy ulnar palsy were found in 5 patients; 1 patient had paresthesias in the distribution of the lateral femoral cutaneous nerve, with a loss of sensation in this distribution. In another patient, examination revealed the signs and symptoms of so-called femoral neuropathy.

An additional 4 patients not heretofore discussed had electromyographic evidence which was suggestive of mononeuropathy, but related abnormality was not uncovered during clinical examination. The latter patients, in the final analysis, were judged to have incomplete or equivocal evidence of neuropathy (Table 1).

Thus, in the group of 43 diabetic patients who had what was considered unequivocal evidence of neuropathy, 27 had diffuse polyneuropathy, 12 had mononeuropathy, and 4 had both mononeuropathy and diffuse polyneuropathy.

Comparison of electromyographic and clinical data. Analysis of the results of clinical and electromyographic examinations of the patients with neuropathy reveals the following correlation between the 2 groups of data, which had been obtained independently.

TABLE 2

CORRELATION BETWEEN ELECTROMYOGRAPHIC AND NEUROLOGIC STUDIES: 31 DIABETIC PATIENTS WITH DIFFUSE POLYNEUROPATHY AND 12 WITH MONONEUROPATHY

Findings	*Polyneuropathy*	*Mononeuropathy*
Clinical only	1	4
Electromyographic and clinical	29	4
Electromyographic only	1	4
None	0	0

Of the 31 patients for whom the diagnosis of diffuse polyneuropathy was made (Table 2), 29 were considered by both electromyographic and clinical criteria to have polyneuropathy. The 2 remaining patients manifested abnormality during only 1 of the examinations; 1 patient who gave no electromyographic evidence of polyneuropathy and whom we included in this group had absent Achilles reflexes with diminished vibratory sensation at the ankles and symptoms of neuropathy, although the patient was only 39 years old. The other patient had no clinical evidence of neuropathy, but, on electromyographic examination, denervation in the anterior tibial, gastrocnemius, and extensor digitorum brevis muscles bilaterally was found; however, studies of nerve conduction gave normal results.

In the 12 patients with mononeuropathy, the correlation between results of the electromyographic examination and results of the neurologic examination was poor (Table 2). In 4 of these patients, there was evidence of mononeuropathy during clinical examination alone. In 1 of these patients, the clinicial observations and symptoms were diagnostic of ulnar neuropathy, but this ulnar nerve had not been tested by the electromyographer. In 1 patient, there was good clinical evidence of median thenar neuropathy, but there was insufficient evidence in the electromyogram for confirmation of the diagnosis. The lateral femoral cutaneous nerve has no motor function and was not studied electromyographically. Thus, data concerning the patient with meralgia paresthesia were not included in the electromyographic data. Finally, in the patient with "femoral" neuropathy, the femoral nerve was not studied electromyographically, but, during clinical examination, quadriceps weakness and sensory dysesthesia over the anterior aspect of the thigh were noted, and the quadriceps reflex was absent.

In an additional 4 patients, there was evidence of mononeuropathy in the electromyographic study alone. In 1 patient, the action

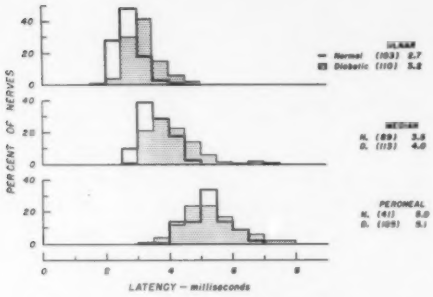

Fig. 1. Latency of response of muscle to maximal stimulation of its motor nerve. Stimulus was applied at wrist for ulnar and median nerves and at ankle for peroneal nerve. Latency represents number of milliseconds elapsing between start of stimulus and beginning of action potential of hypothenar muscles (ulnar nerve), thenar muscles (median nerve), or extensor digitorum brevis (peroneal nerve).

potential of the left thenar muscles was of low amplitude, and the latency of the response to stimulation of the median nerve was prolonged, indicating abnormality of the median nerve. In addition, fibrillation potentials were observed in the muscles innervated by the median nerve. Similar observations in the electromyographic study indicated abnormality of the peroneal nerve of 2 patients and of the ulnar nerve in an additional patient.

Analysis of the data concerning the 13 patients whose condition we called "equivocal" revealed that in all of them there was suggestive evidence of neuropathy in the electromyogram; 4 exhibited equivocal evidence of neuropathy during the clinical examination as well.

Clinical aspects. The clinical observations among the 31 patients with polyneuropathy included absent or diminished gastrocnemius reflexes with diminution of vibratory sensation at the ankles. These observations were made in all but one of the patients included in the group described as having polyneuropathy. Loss of tactile sensibility, impairment of 2-point discrimination, and weakness also were found in these patients. No attempt was made to measure autonomic function in this study; 8 of the men did report impotence. Nocturnal diarrhea was reported by 2 patients and symptoms of postural hypotension by 18 patients. Pupillary irregularities occasionally were observed, but in no patient did these fulfill the classic description of the Argyll Robertson pupil.

Electromyographic aspects. Studies of nerve conduction in the 103 diabetic patients showed

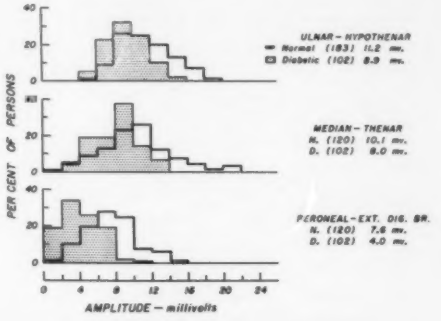

Fig. 2. Amplitude of action potential evoked in hypothenar, thenar, and extensor digitorum brevis muscles by single maximal stimulus applied percutaneously to ulnar, median, and peroneal nerves, respectively. Amplitude of principal negative spike evoked by stimulation of nerve at elbow or knee was measured. Surface electrodes placed over belly and tendon of muscles were used to detect action potential.

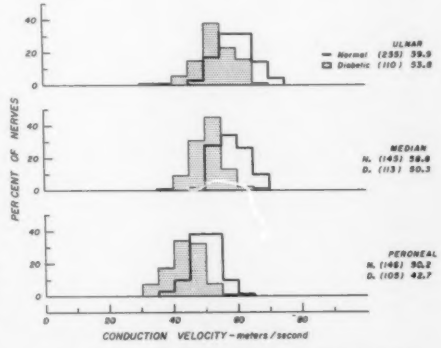

Fig. 3. Conduction velocity of motor fibers of ulnar, median, and peroneal nerves in healthy persons and patients with diabetes mellitus. Conduction velocity in segment of nerve between elbow and wrist (ulnar and median nerves) or knee and ankle (peroneal nerve) was measured.

that the average latency of the motor response to stimulation of the ulnar and median nerves at the wrist was slightly longer than that in healthy persons (Fig. 1). Similarly, the average amplitude of the muscle-action potential in these diabetic patients was lower than similar measurements in normal persons (Fig. 2).

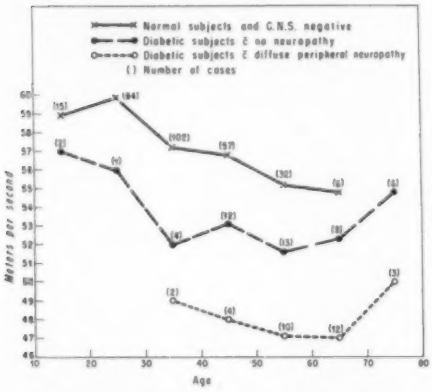
Normal subjects and C.N.S. negative
Diabetic subjects & no neuropathy
Diabetic subjects & diffuse peripheral neuropathy
( ) Number of cases
Meters per second
Age

Fig. 4. Conduction velocity of motor fibers of median nerve between elbow and wrist, as related to age

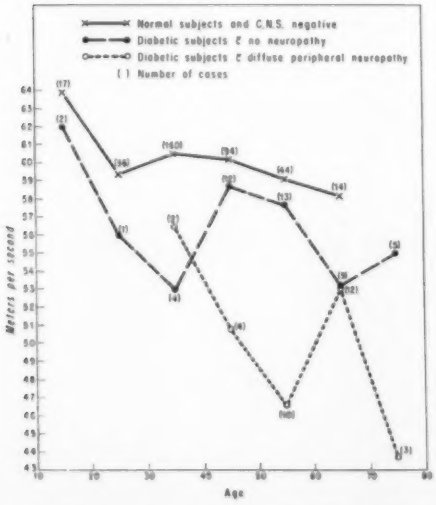
Normal subjects and C.N.S. negative
Diabetic subjects & no neuropathy
Diabetic subjects & diffuse peripheral neuropathy
( ) Number of cases
Meters per second
Age

Fig. 5. Conduction velocity of motor fibers of ulnar nerve between elbow and wrist, as related to age

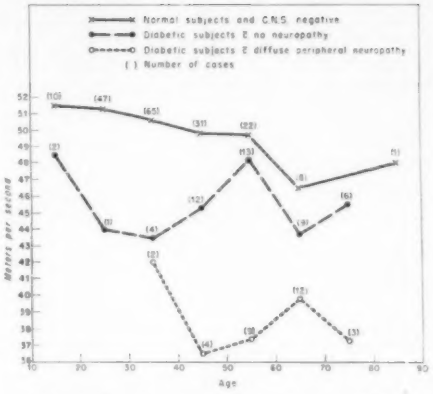
Normal subjects and C.N.S. negative
Diabetic subjects & no neuropathy
Diabetic subjects & diffuse peripheral neuropathy
( ) Number of cases
Meters per second
Age

Fig. 6. Conduction velocity of motor fibers of peroneal nerve between knee and ankle, as related to age

The conduction velocity of the motor nerves (elbow to wrist or knee to ankle) in the 103 patients on the average was slowed. In the diabetic patients, the averages were ulnar nerve, 53.8 meters per second; median, 50.3 meters per second; and peroneal, 42.7 meters per second. Similar figures for healthy persons in our experience are ulnar nerve, 59.9 meters per second; median, 58.8 meters per second; and peroneal, 50.2 meters per second (Fig. 3).

The possibility was studied that the decreased average conduction velocity might be related to a lowered temperature of the extremity in which the studies of conduction velocity were made or that this decrease might be related to the average older age of the diabetic patients. Muscle temperatures, determined by the use of a thermistor in the tip of a needle which was inserted into the first dorsal interosseus muscle, revealed no correlation between the observed slowing of conduction in the distal part of the nerve and a lowered temperature in the hand. A comparison of the conduction velocity of the peripheral nerves in the 31 diabetic patients with polyneuropathy, the 47 diabetic patients whom we classified as "normal" with respect to neuropathy, and healthy persons examined in the electromyographic laboratory was made according to

decade of life (Figs. 4 through 6). It was found that the 31 patients with polyneuropathy had a slowing of conduction velocity of about 5 to 12 meters per second below the averages for normal persons of similar age. This abnormality was most marked in the peroneal nerve. In the 47 "neurologically normal" diabetic patients included in this study, the average conduction velocity also was slow, but by a lesser amount. Few patients in the latter group had conduction velocities above the averages established for healthy persons in similar age groups. Further analysis of the electromyographic data revealed that fibrillation potentials were observed in some muscles of 25 of the 103 diabetic patients.

COMMENT

Clinical signs and electromyographic evidence of neuropathy were common in this group of 103 unselected ambulatory diabetic patients; 43 had unequivocal evidence of neuropathy. In a general way, the neuropathy was more common among older diabetic patients, those with more severe diabetes as measured by insulin requirements, and those who had had the disease for the longest time (Table 1). However, symptoms of neuropathy were the presenting complaint of some patients with newly discovered diabetes in this series as well as in other reported series.[3] In this series, 8 of the 24 patients newly discovered to have diabetes were found to have neuropathy. By contrast, many patients have severe diabetes for decades with no objective evidence of neuropathy. Neither was there a significant correlation between estimated control of diabetes and the presence of neuropathy. For example, 1 of our patients had had severe, poorly controlled diabetes for sixteen years, necessitating more than 100 units of insulin a day. Neurologic examination revealed no abnormalities, and the studies of nerve stimulation demonstrated conduction velocities of 53 meters per second for the ulnar nerve, 45 meters per second for the median nerve, and 42 meters per second for the peroneal nerve.

Patients with neuropathy can be classified readily as those with polyneuropathy and those with mononeuropathy. Among the 31 patients with diabetic polyneuropathy, predominantly distal and symmetric findings were most marked in the lower extremities. Clinically, the most striking feature was diminution of the gastrocnemius reflexes and vibratory sensation at the ankles. The conduction velocity of the peripheral nerves was diminished, usually by 5 to 12 meters per second, and the latency of response and the amplitude of the muscle-action potential evoked by motor stimulation of the nerves were abnormal in most patients. In 2 patients, neuropathy was associated with Kimmelstiel-Wilson disease. More than half of the 31 patients with polyneuropathy had evidence of diabetic retinopathy, as reported by Dr. C. Wilbur Rucker of the Section of Ophthalmology, while only 10% of the 47 patients we had classified as "normal" in respect to neuropathy had similar retinal changes. The higher incidence of renal changes and retinopathy in the patients with overt neuropathy supports the longheld belief that there are etiologic similarities among the 3 complications of diabetes. However, there was not a similar correlation in this series of patients between polyneuropathy and arterial changes as palpated in peripheral arteries or as evidenced by coronary arterial disease.[4]

The mononeuropathies[5] were similar to those we have discussed elsewhere as autogenous mononeuropathy.[6] In most instances, the peripheral nerve was injured at some local vulnerable site as it passed over a bony prominence (peroneal and ulnar) or through a ligamentous and bony tunnel (median). Such injuries to peripheral nerves were more common in these diabetic patients than in similar patients without diabetes, but they responded identically to appropriate therapy.[5]

Femoral neuropathy was found in 1 patient. This neuropathy often is a lesion of the upper lumbar plexus or a radiculitis rather than a single nerve lesion. We have recently reported upon 19 patients with such a neuropathy,[7] 14 of whom had diabetes. In our experience, onset of this type of neuropathy is often abrupt, followed by a gradual return of function over a period of several weeks to months. The clinical course of this syndrome as well as that of other asymmetric peripheral neuropathies with similar onset and of the oculomotor palsies associated with diabetes

suggests the possibility that they are vascular in origin. Woltman and Wilder,[8] Dreyfus, Hakim, and Adams,[9] and Fagerberg[10] have presented pathologic data suggesting that in some patients diabetic neuropathy may be ischemic in origin.

Thus, in diabetic patients with mononeuropathy, the clinical course often is remitting, and the precipitating causation of the neuropathy appears to be local. The origin of these local alterations in nerve function may be traumatic or vascular.

Exogenous hyperinsulinism[11] is an additional rare cause of neuropathy in diabetic patients. This type of neuropathy is primarily motor, distal, and symmetric. The onset is associated with profound hyperinsulinism, and the neuropathy tends to abate once the hyperinsulinism has been corrected. No patient with this syndrome was observed during the course of the study.

Data obtained by clinical and electromyographic examination in patients eventually found to have polyneuropathy revealed a high correlation between the results of these 2 dissimilar methods of study carried out independently. On the other hand, among the patients for whom the diagnosis of mononeuropathy was made, comparison of the data obtained by these 2 methods of study revealed discrepancies. Absence of confirmatory electromyographic observations in patients with mononeuropathy was noted when the neuropathy was primarily sensory or, of course, when the specific nerve involved had not been tested.

The failure of the clinical examination in some instances to disclose neuropathy in this study seems related to the crudeness of clinical methods. Most of the patients whose condition was included in the category of questionable neuropathy exhibited abnormalities only during the electromyographic evaluation. This also suggests that the latter method of examination sometimes is a more sensitive detector of abnormal function in the peripheral nerves than is the clinical examination. The electromyogram in this study has provided us with a sensitive and reproducible method of measuring altered function in the peripheral nerves of diabetic patients.

This study again demonstrates the need for careful cooperation between the neurologist and the electromyographer. It is not possible to study in each patient all muscles and all nerves electromyographically, and hence some selection of the areas to be examined must be made. If such cooperation had not been prevented by the plan of this study, all the clinically affected nerves could have been studied with appropriate electromyographic technics, and confirmatory electromyographic evidence of neuropathy might have been found in some patients with clinical evidence of neuropathy whose electromyographic pattern had been reported as normal. The electromyogram is perhaps most effective as an extension of the neurologic examination. It has the advantages of being more sensitive to alteration of function in the motor unit and of providing the clinician with data which are more reproducible than the observations made at clinical examination.

In a comparison of the electromyographic findings in the 103 diabetic patients (Figs. 1 through 6) with those of healthy persons,[12] we noted a general shift in the distribution of mean values toward slower conduction and a lower amplitude of response in the diabetic patient. Few of the diabetic patients yielded values above the mean of the normal range. The data suggest that, even among the 47 diabetic patients in whom no neuropathy was found, there was, on the average, some alteration of nerve function. This over-all change was not related to lower temperatures in the extremities of the diabetic patients.

To evaluate the influence of age, nerve conduction in the 47 diabetic patients in whom we found no clinical evidence of neuropathy was compared with that in the 31 diabetic patients with polyneuropathy and that in a group of healthy subjects (Figs. 4 through 6). In this comparison, patients in each group were divided according to age by decade. The conduction velocity of the nerves in the diabetic patients without neuropathy was, on the average, consistently less (mean, 3.7 meters per second) than our normal values, although not to the degree found in diabetic patients with neuropathy (mean, 8.6 meters per second). These changes were apparent in all

decades of life, and it is therefore assumed that the preponderance of older persons among diabetic patients did not account for the slowing.

It should be noted that selected patients with diabetic neuropathy who have been referred because of neurologic complications have exhibited greater abnormalities in the electromyogram and in conduction velocity than those seen in the present unselected group of patients. The former group of patients will be the subject of a later report.

Others have described a disturbance in the peripheral nerves of nearly all diabetic patients. Barach,[13] Collens, Zilinsky, and Boas,[14] and Mirsky[15] have reported a significant increase in the threshold for vibratory sensation in a high proportion of diabetic patients. More recently, Eliasson[16] has reported definite slowing of peripheral-nerve conduction in rats soon after the induction of diabetes with alloxan. We would postulate that such changes may be an expression of an alteration in the peripheral nerves of diabetic patients which enhances the vulnerability of the peripheral nerves to various kinds of trauma.

Such an increase in the sensitivity of peripheral nerves might explain the frequency of mononeuropathy or the ease with which neuropathy is precipitated in diabetic patients.[17]

The finding of polyneuropathy in some patients with newly discovered mild diabetes again raises questions regarding the role of inadequate control of the carbohydrate defect of diabetes in the pathogenesis of neuropathy.[18-20] Precise data on the degree and duration of the carbohydrate defect and the accuracy of its control are notoriously hard to obtain. The present data suggest, but do not prove, that inadequate control of sugar in the blood and urine is not the sole determinant in the pathogenesis of polyneuropathy, and that there may be other factors of importance. Except in the mononeuropathies, in which local, traumatic, or vascular influences seem to play an important role, the nature of other possible factors remains obscure. However, there is no question about the desirability of controlling the carbohydrate defect as well as possible until other etiologic factors are identified.

The frequent association, in this series, as in others,[21] of neuropathy and retinopathy emphasizes again the possibility of a common causation for both these complications. Possibly, there is simply a concurrent relationship between these complications and the disturbance of carbohydrate metabolism, resembling the relationship between the anemia and changes in the spinal cord in the presence of pernicious anemia, in which the two manifestations of the same disease may be associated but are of different severity and respond in a dissimilar manner to therapy. It is apparent that at present the basic pathophysiology of degenerative complications of diabetes is a matter for speculation and that a logical treatment for diabetic polyneuropathy awaits a better understanding of the cause of this disease. On the other hand, the diabetic mononeuropathies frequently disappear or abate when the local precipitating cause is removed.[21]

SUMMARY

A total of 103 unselected diabetic patients were studied independently in the electromyographic laboratory and by clinical neurologic examination. In 43 of these patients, the findings of neuropathy were unequivocal. A comparison of the electromyographic and clinical findings arrived at independently revealed a most complete agreement between the 2 when a diagnosis of polyneuropathy was made. The discrepancies observed in the diagnosis of mononeuropathy were related to the occasional failure to select the involved nerve or muscle for test by the electromyographer, who in this study worked without a preliminary neurologic examination, and to the greater sensitivity of the electromyographic examination in the nerves and muscles which were tested. The advantages of the electromyogram included its greater sensitivity to nerve changes and its ability to measure alterations of nerve function in a reproducible manner.

The neuropathies encountered included both mononeuropathy and polyneuropathy. The former included those neuropathies which we have previously called "autogenous" and which are amenable to specific therapy, and

femoral neuropathy, which in our experience is a self-limiting disturbance. The polyneuropathies were found most commonly in patients with long-standing and severe diabetes. However, polyneuropathy occasionally was seen in patients with newly discovered mild diabetes, and it may not be present in patients with severe, poorly controlled diabetes of long duration.

Studies of nerve conduction revealed slowing of conduction in most of these patients as measured by the tests used.

These studies suggest that there may be alteration in the peripheral nerves of diabetic patients without overt neuropathy as well as in those with neuropathy (Figs. 4, 5, and 6). It is suggested that this alteration of peripheral nerves may be accompanied by an increased vulnerability of the nerves, which in some patients is expressed by polyneuropathy and in others, when the stress is local, by mononeuropathy.

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Electron microscopic observations on subarachnoid and perivascular spaces of the Syrian hamster brain

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THE PROBLEM of identifying the various spaces in the central nervous system, determining their relationships to each other, and estimating their functional significance has occupied investigators since the middle of the last century.[1–7] The considerable literature on this subject has been extensively and critically reviewed by Woollam and Millen.[8] With the higher resolution made possible by the use of the electron microscope, structures unknown or incompletely visualized and relationships previously only theoretic can be clearly shown. It was, therefore, considered of value to study the space problem with the electron microscope, with the hope of clarifying old concepts and correlating the light microscopic observations with what is now known about the fine structural organization of the leptomeninges and blood vessels of the central nervous system.

A few electron microscopists have touched briefly on this subject or published relevant microphotographs.[9–11] Pease and associates have given good descriptions of the rat cranial meninges and also of the small vessels of the rat cortex but have not defined the perivascular space or discussed its relationship to the subarachnoid space. An electron microscopic description of artifacts in the central nervous system which resemble the controversial spaces of classic histology has also not been heretofore mentioned and is of some historic interest. A thorough understanding of these anatomic facts seemed necessary for an intelligent appraisal of pathologic material, and the studies herein reported originated as a necessary preliminary to a detailed investigation of various types of cerebral inflammation.

MATERIAL AND METHODS

Most of the observations were made on cortex and overlying meninges from normal, adult Syrian hamsters (Mesocricetus aureatus). In addition, pathologic material of 2 types was utilized to study the perivascular spaces. Brains from animals which had received massive x-irradiation to the skull were examined, as were specimens from animals injected intracerebrally with 0.05 to 0.1 cc. of a saline suspension of Escherichia coli. The animals were anesthetized with ether, after which the skull was carefully removed. The dura remained adherent to the bone, and, therefore, only fragments of dura were included in the specimen. Small pieces of tissue from the dorsal surface of the cerebral hemispheres were fixed in 2% buffered osmium tetroxide solution, dehydrated, and embedded in methacrylate. In a few animals, fixation was accomplished in situ by decapitation, rapid removal of the skull, and dripping osmium tetroxide solution on the exposed brain surface. Both methods were acceptable, but, with the latter, there was no subarachnoid bleeding.

In order to orient the brain surface in the proper plane for sectioning and to determine optimum areas for electron microscopic study, sections 2 to 3 μ in thickness were examined

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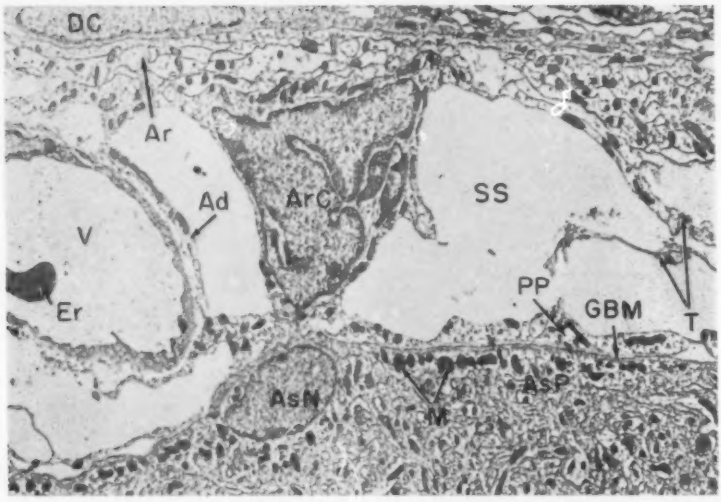

Fig. 1. Cerebral cortex and meninges from normal animal. Note numerous mitochondria (M) in subpial astrocyte process (AsP). Glial basement membrane (GBM) can be seen between pial (PP) and astrocytic processes, particularly where pia has been artificially separated from brain surface. Large arachnoidal cell (ArC) bridges subarachnoid space (SS) and together with pia contributes to adventitia (Ad) of vessel (V). Dural cells (DC) and processes are attached to outer portion of arachnoid (Ar). AsN, astrocyte nucleus; Er, erythrocyte; T, trabeculae. × 4,500

with the phase microscope. Ultrathin sections were cut on either a Leitz or Porter-Blum microtome, picked up on copper grids previously coated with formvar films, and examined in a Siemens electron microscope ÜM 100.

RESULTS

The subarachnoid space. It is not within the scope of this report to describe exhaustively the fine structure of the cerebral surface and its coverings, since these have been considered in detail elsewhere.[11,12] However, their per-

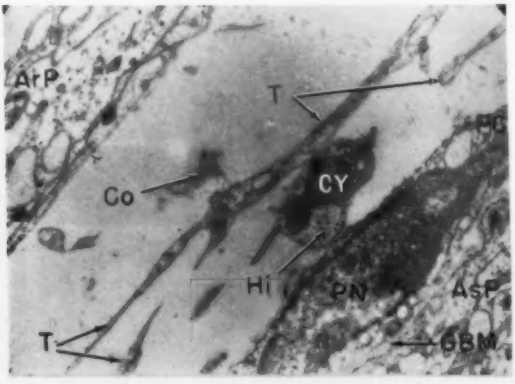

Fig. 2. Cerebral cortex and meninges from normal animal. Successive layers of superficial part of brain and leptomeninges extend diagonally across micrograph. ArP, arachnoid processes; Co, collagen fibrils; Hi, histiocyte; Cy, cytosome; T, trabeculae; PN, pial nucleus; PC, pial cytoplasm; GBM, glial basement membrane; AsP, astrocytic process. × 7,200

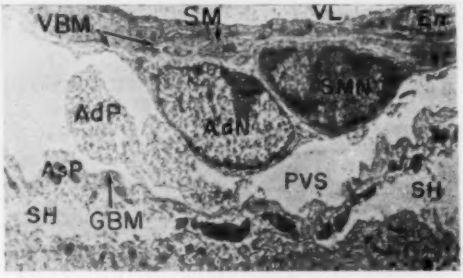

Fig. 3. Small artery in cerebral cortex of normal animal. Several small profiles of smooth muscle cells (SM) and one large, centrally cut muscle nucleus (SMN) are completely enclosed by vascular basement membrane (VBM) continuous with that of endothelium (En). Less dense adventitial cell nucleus (AdN) and cytoplasmic processes lie within perivascular space (PVS) along with process from another similar cell (ADP). On both sides of midline, astrocytic processes (AsP) have been artificially torn, producing artifactitious space of His or Held (SH). VL, vessel lumen; GBM, glial basement membrane. × 4,500

tinent cytologic and histologic relationships must be mentioned here.

The surface of the cerebral cortex is made up of an apparently complete layer of glial processes which also follows penetrating vessels into the brain. These processes overlap and interdigitate to a variable extent, but the most superficial layer can often be followed for several microns (Fig. 1). The cytoplasm of these cells is somewhat pale, due chiefly to the low density of their ground substance and relatively sparse ribonucleic acid granules. Within the cytoplasm occur poorly circumscribed groups of fine filamentous structures, which are particularly prominent near the external margins of the cells and are considered to be astrocytic fibrils (Fig. 4). The mitochondria in these subpial astrocytes are remarkable in that these organelles often appear unusually numerous and large and sometimes contain longitudinal striations instead of the customary transverse mitochondrial crests. Intracytoplasmic inclusions, some of which probably contain lipid, are also noted in normal preparations. Intimately associated with the astrocytic layer is a well-defined, continuous, osmiophilic

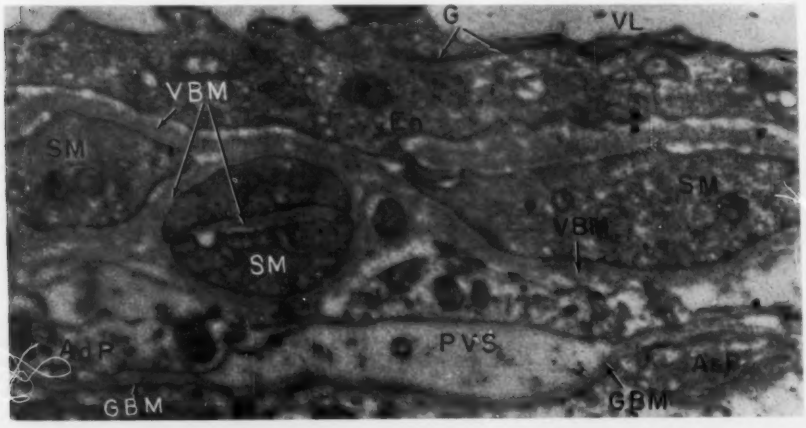

Fig. 4. Small artery in cerebral cortex of normal animal. Continuous vascular basement membrane–elastin complex (VBM) separates endothelium (En) and individual smooth muscle cells (SM) and, together with glial basement membrane (GBM), forms boundaries of perivascular space (PVS), which here contains a single longitudinally cut adventitial process (AdP) and a few very delicate similar processes seen in cross section. VL, vessel lumen; G, gap between 2 overlapping endothelial cells; AsF, astrocytic fibers. × 21,600

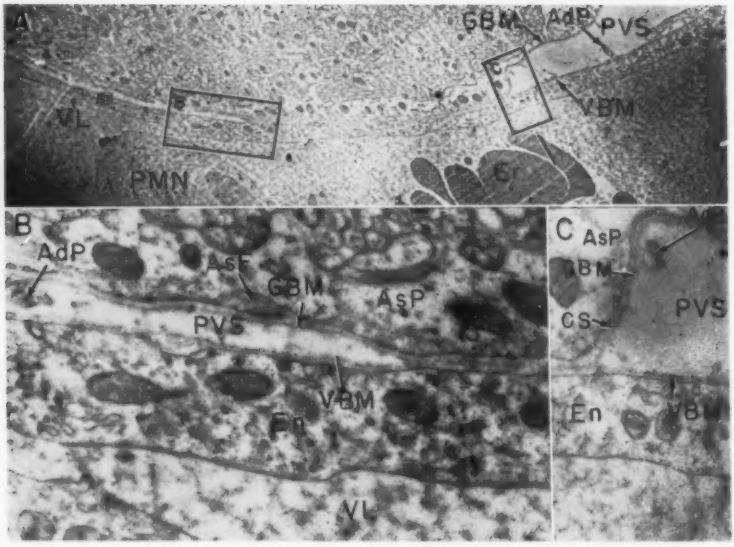

Fig. 5. Vein from cerebral cortex of normal animal. In midportion of A, vascular (VBM) and glial (GBM) basement membranes have become confluent, forming a broader complex and obliterating perivascular space (PVS) which, on both left and right sides of micrograph, is patent and contains a few delicate adventitial processes (AdP). B and C are higher magnifications of areas where basement membranes merge, as outlined in A. Transluscent band of "cement substance" (CS) between osmiophilic basement membrane and endothelial or glial cell membranes can here be clearly seen. VL, vessel lumen; Er, erythrocyte; PMN, polymorphonuclear leucocyte; AsP, astrocyte process; En, endothelium; AsF, astrocyte fibrils. A, × 4,500; B and C, × 21,600

basement membrane, separated from the astrocytic boundary by an electron transluscent band (Figs. 1, 2, and 5). The basement membrane bridges cell boundaries, while the relatively transluscent region can, in some areas, be observed to be continuous with the narrow intercellular space which separates adjacent glial and neuronal cells and their processes in the brain.

The pial cells vary in appearance but, in their usual form, are irregularly oval with several very long and delicate processes, some of which are in apposition with arachnoidal tissue (Fig. 2). In most of the normal preparations, the brain surface seems to be covered by a single layer of these delicate cytoplasmic extensions, which overlap only slightly. Occasionally, but not always, the pial processes extend over a penetrating blood vessel, and, in these regions, it is not possible to make a clear-cut distinction between pial and adventitial tissue (Fig. 1). In the normal situation, with an intact pial covering, the astrocytic basement membrane is shared by the pial cells. The endoplasmic reticulum of the pial cell is prominent and often widened into vesicles of varying sizes. Even in the normal animal, a few "cytosomes" or "dense bodies"[13,14] and intracytoplasmic inclusions are sometimes noted. The external boundary of the subarachnoid space is made up of cells which are essentially similar to those of the pia. However, in the arachnoid, the numerous, finger-like cytoplasmic extensions overlap and interdigitate to a marked degree, so that this membrane is actually many cell processes thick.

The subarachnoid space, defined, as is customary, as that space lying between the arach-

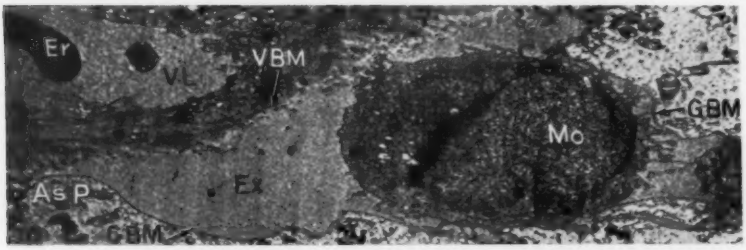

Fig. 6. Small artery from white matter of animal that received 15,000 r to skull forty-five hours before sacrifice. Layers of vessel wall cannot be defined at this magnification because of tangential sectioning. Within perivascular space is an exudate (Ex), with structureless appearance and density resembling intravascular plasma. Glial (GBM) and vascular (VBM) basement membranes can be recognized even at this low magnification. VL, vessel lumen; Er, erythrocyte; Mo, monocyte lying within exudate in perivascular space; AsP, astrocyte process. × 4,500

noid and pial membranes, is irregular in width and is traversed by numerous fine trabeculae derived from either pial or arachnoidal cells. One or more leptomeningeal cells occasionally bridge the subarachnoid space (Fig. 1). Within leptomeningeal tissue occur small pockets or cisterns which communicate with the subarachnoid space. Collagen fibrils, often gathered into bundles, are seen both adjacent to the leptomeningeal cell processes and lying free within the subarachnoid space (Fig. 2). A few large, irregularly shaped histiocytes containing numerous vesicles and prominent, dilated endoplasmic reticulum as well as cytosomes and other inclusions can also be found within the subarachnoid space of normal animals (Fig. 2).

The composition of the blood vessels in the subarachnoid and perivascular spaces can be particularly well appreciated in electron microscopic preparations (Figs. 1, 3, and 4). The endothelial layer of an artery is surrounded by a well-defined basement membrane which is, in turn, covered by one or more layers of circularly arranged smooth muscle. These smooth muscle cells are completely enclosed by a basement membrane which is continuous with that of the endothelium. In the interstitial space between the components of the tunica media and the tunica intima, and sometimes incorporated into their basement membranes, is the internal elastic membrane which we, in agreement with the observations of Pease and Molinari,[15] could not clearly distinguish from the basement membrane in simple osmium-fixed material. The adventitial layer is made up of cells which, except for their location and the loose application of their processes to the vessel wall, are quite similar in appearance to leptomeningeal cells. Veins, though possessing wide lumens, are often extremely thin-walled, consisting only of endothelium, basement membrane, and a single delicate layer of adventitial cytoplasm.

The perivascular space. Observations on the penetrating vessels and their relationship to the perivascular and subarachnoid spaces have been limited to small arteries and veins. It has been consistently noted that the layer of superficial astrocytic processes and their overlying basement membrane seem to follow and surround the vessel as it enters cerebral tissue. The glial basement membrane is separated from that of the smooth muscle cells or endothelium by adventitial cells or their processes. The space lying between the glial and vascular basement membranes is considered to be the true perivascular space (Figs. 3 through 10). When adventitial elements disappear, the 2 basement membranes merge and a perivascular space no longer exists. Occasionally, the confluent basement membranes continue for a short distance and then diverge, producing again a perivascular space which contains adventitial components (Fig. 5). However, it has not been determined that such an obliter-

ation of the perivascular space occurs along the entire circumference of the vessel at this point. In normal preparations, this space may be completely filled by one or more adventitial cells or may appear relatively empty and contain only delicate adventitial processes and scattered bundles of colagen fibrils. Such a perivascular space has been seen not only in the superficial layers of the cerebral cortex but also in the granular layer of the cerebellum and in the cerebral white matter.

At the capillary level, there exists no perivascular space and only a basement membrane lies between endothelial or so-called "pericyte"[9] cytoplasm and adjacent, predominantly astrocytic processes. In our preparations, this basement membrane usually appears homogenous, so that osmiophilic and transluscent layers cannot be distinguished. Surrounding the capillaries, the astrocytic border is no longer complete, and oligodendroglial and neuronal processes are also seen perivascularly.

The perivascular space has also been studied under pathologic conditions. After massive local x-irradiation, there is an extensive plasma exudation into the perivascular space. In the early stages, the exudate is confined between the glial and vascular basement membranes, often in association with inflammatory cells (Fig. 6). Later, macrophages occur in the same location (Fig. 8). Identical relationships are seen around superficial cortical vessels in animals with experimental cerebral infection, where polymorphonuclear leukocytes, proliferating fibroblasts, histiocytes, and bacteria have also been observed within this perivascular space (Fig. 7).

Artifactitious spaces. In a few preparations, an irregular widening of the astrocytic cytoplasm beneath the pia and around the vessels is seen. Here, there is relative preservation of the protoplasmic structure and organelles near the basement membranes, with rarefaction of the remainder of the cytoplasm. Often, adja-

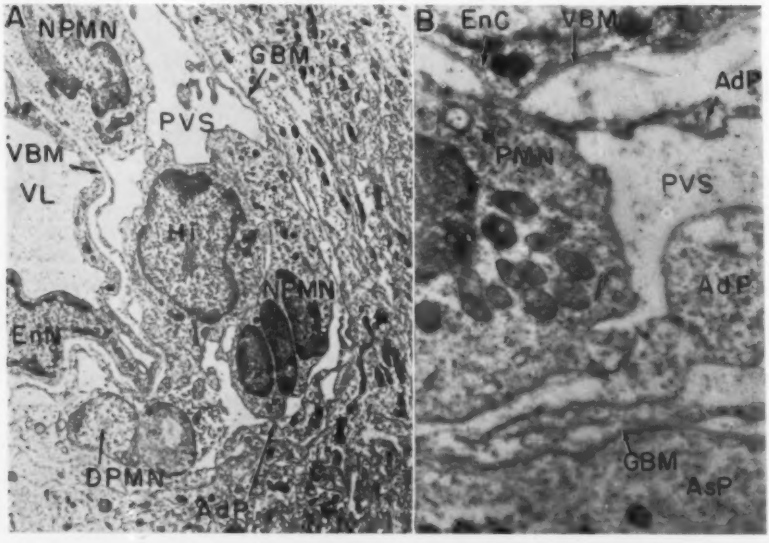

Fig. 7. Small vein in cortex of animal injected intracerebrally with suspension of E. coli three days before sacrifice. In A, perivascular space (PVS) between vascular (VBM) and glial (GBM) basement membranes contains normal (NPMN) and degenerating (DPMN) polymorphonuclear leukocytes, adventitial processes (AdP), and a histiocyte (Hi). In B, portion of same leukocyte seen in upper left corner of A is shown at higher magnification. VL, vessel lumen; EnN, endothelial nucleus; EnC, endothelial cytoplasm; AsP, astrocyte process. A, × 4,500; B, × 14,400

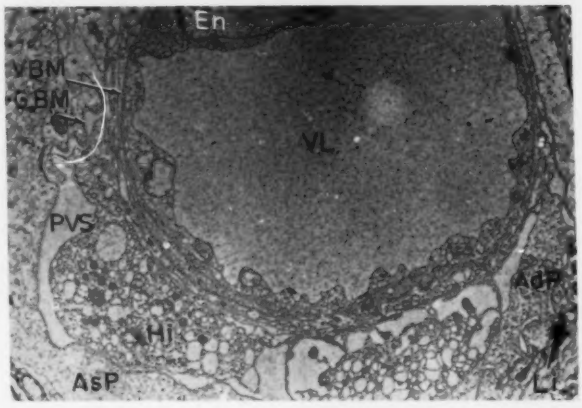

Fig. 8. Small vein from white matter of animal which had received 45,000 r to skull one hundred forty hours before sacrifice. VL, vessel lumen; VBM, vascular basement membrane; GBM, glial basement membrane; Hi, histiocyte; AdP, adventitial process; AsP, astrocyte process; Li, lipid in astrocyte process; En, endothelium; PVS, perivascular space. × 4,500

cent astrocytic membranes are disrupted so that relatively extensive, artificial, unstructured clefts can occur in the subpial and perivascular glial margins and also extend into deeper portions of the cerebral tissue (Figs. 3 and 9).

DISCUSSION

As has been noted in several electron microscopic investigations, the most superficial portion of the brain is composed of astrocytic processes.[9,11,16,17] Perivascular[18] and subpial gial processes have been observed to contain delicate intracytoplasmic fibrils and can reasonably be considered to represent the fibrous astrocytes described in these regions by light microscopists.[19] Both their cytologic structure with intracellular fibrils and their location argue against the identification of this cell type as oligodendrogliocytes, as has been maintained by some investigators.[20,21] The basement membrane of the marginal glia has the same appearance as basement membranes in a variety of locations[22,23] and can also be considered to be made up of mucopolysaccharide.[23,24] According to the conceptions of Pease,[23] the osmiophilic band represents the true basement membrane, while the lighter region which lies between this structure and the overlying cell membrane can properly be termed "cement" substance and probably also contains a polysaccharide component. This lighter band is continuous with the intercellular or "gap" substance of Robertson[25] that is contained in the 150 to 200 Å space that

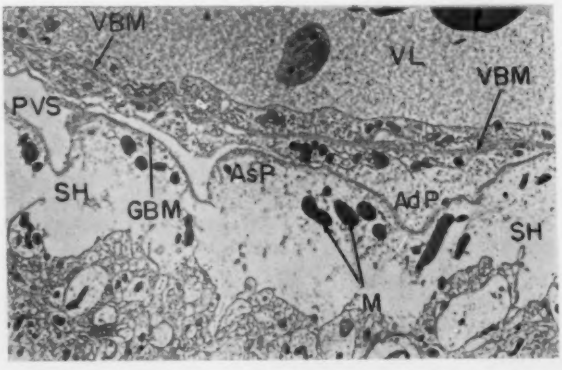

Fig. 9. Vein from cerebral cortex of normal animal. Within perivascular space (PVS) lies single delicate adventitial process (AdP). Artifactitious space (SH) is situated within disrupted astrocytic processes (AsP) and is therefore separated from true perivascular space by glial basement membrane (GBM). VL, vessel lumen; VBM, vascular basement membrane; M, mitochondria in astrocyte process. × 4,500

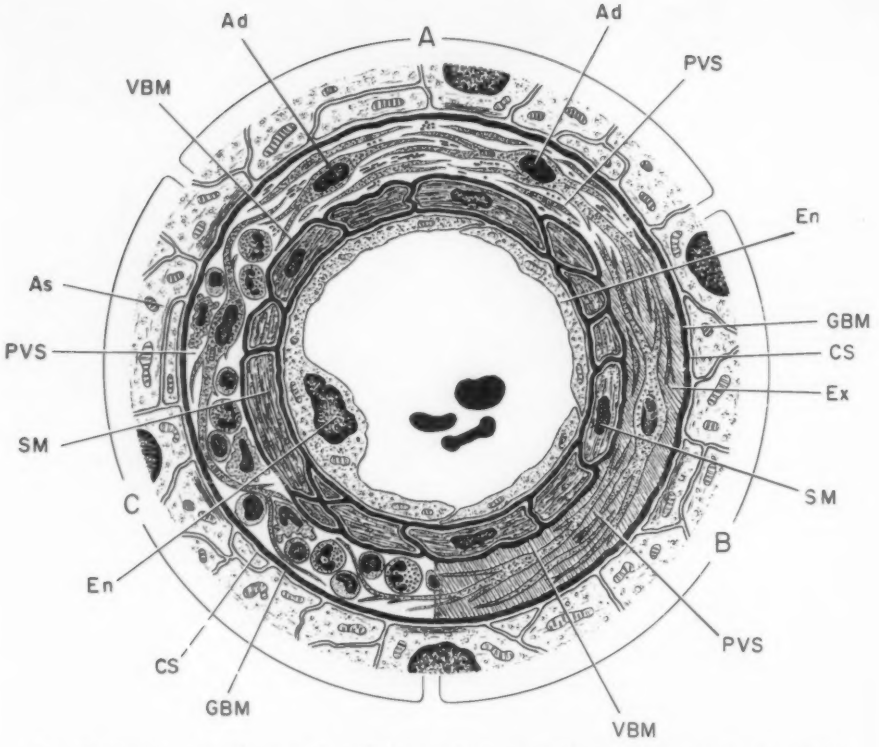

Fig. 10. Semischematic diagram of small intracerebral artery showing perivascular space (PVS) under normal and pathologic conditions and containing in A, normal adventitial cells (Ad); in B, exudate (Ex); and in C, inflammatory cells. Perivascular space is bounded by vascular basement membrane–elastin complex (VBM) that surrounds endothelium (En) and smooth muscle cells (SM) and by glial basement membrane (GBM) of marginal astrocytes (As). Light band between dark basement membrane and adjacent cell membranes represents "cement substance" (CS) of Pease.

separates the glial and/or neuronal processes in the central nervous system. It should be emphasized that, in the brain, this gap is the only morphologically extracellular space[26,27] and should be distinguished from the "interstitial space," which is a term applicable only to the subarachnoid or perivascular spaces.

The presence of a basement membrane on the surface of the brain is not particularly remarkable in view of the frequent occurrence of such a structure at the margin between various types of cells and other broad, interstitial spaces. Similar relationships have been described in several tissues, including smooth muscle, peripheral nerve, Auerbach's plexus, and kidney.[22,23,28] One can only speculate as to the role of the basement membrane as a brain covering; however, it is reasonable to consider it as having a supportive function and, together with underlying glial processes, acting as a barrier between brain and cerebrospinal fluid. The ancient term "membrana limitans gliae" introduced by Held[29] might still be retained in a restricted form to refer to the basement membrane–glial cell membrane complex.

The appearance of the leptomeningeal cells and their relationship to adjacent structures is essentially similar to that described by Pease and Schultz,[11] except that we have not consistently observed pial processes covering penetrating vessels or following these vessels into the brain. The trabeculae, easily noted with the light microscope, can, with higher resolution, be positively identified as pial or arachnoidal cell processes. Bundles of collagen fibrils seem to occupy no special location and simply lie extracellularly in the subarachnoid space. The origin of the free histiocytes seen in normal material cannot be established with certainty, but, in experimental meningitis,[30] pial cells and probably also adventitial cells can be transformed into macrophages.

Some of the confusion concerning the perivascular spaces of the central nervous system has disappeared since the publications of Patek[6] and Woollam and Millen.[8,31] These investigators, by injecting indicator substances into the subarachnoid space and utilizing good histologic technic, clearly distinguished between real and artifactitious spaces. Particularly important for modern investigations of this problem is the recognition that a great deal of the early work was done employing widely varying technics and unstandardized terminology. It is, therefore, both unfair and inaccurate to criticize or draw far-reaching conclusions from much of the early literature. However, even in recent years, there still exists considerable disagreement about the composition of the boundaries and the extent and even the existence of the perivascular space.[6,8,10,31] Probably the most generally accepted concept concerning this controversial problem has been as follows: Just external to the rather meager adventitia of the cerebral vessels is an "inner" reticular sheath derived from the arachnoid. The true perivascular space is in communication with the subarachnoid space and lies between the loose connective tissue envelopes consisting of this "inner" reticular sheath and an "outer" reticular sheath derived from the pia and in contact with the marginal glia. At some uncertain point, the two reticular perivascular sheaths come together, thus obliterating the space. The single perivascular sheath continues for a variable distance, "fading away into the surrounding parenchyma as the smaller vessels are reached."[8] This conception of the perivascular space is largely derived from studies on the fate of particulate matter injected into the subarachnoid space and is chiefly based on an examination of vessels with a well-defined connective tissue layer. Our observations on this subject are limited both in that they have been made on a single species of rodent and that they are based on study of relatively small and thin-walled arteries and veins. Nonetheless, it seems probable that they would be applicable to higher mammals as well, and valid regardless of the caliber of the vessel or the width of its wall. It is, therefore, proposed that the true perivascular space might be simply redefined as that space around a blood vessel bounded internally by the continuous basement membrane of the tunica media or intima and externally by the glial basement membrane and containing connective tissue elements (Fig. 10). Under normal circumstances, one or more adventitial cells or their processes occur in the perivascular space. We have not yet seen consistently significant ultrastructural differences between adventitial cells and the cells of the leptomeninges and have not found a reticular perivascular sheath distinct from that of the adventitia.

Under pathologic conditions, inflammatory or reactive cells, exudate, and bacteria are also seen within the perivascular space.[30] The glial basement membrane apparently tends to limit the extent of the perivascular inflammatory reaction, thus producing the well-circumscribed perivascular "cuffing" so familiar to neuropathologists (Figs. 7 and 10).

The apparently constant presence of adventitial elements in the space between the two basement membranes would seem to rule out the possibility that it is artificially produced; however, the width of the space might well be influenced by methods of preparation.

In most of our specimens, there was, for at least several microns, a free communication between subarachnoid and perivascular spaces. However, around some vessels, the perivascular space was obliterated near the brain surface by a confluence of the two basement membranes, only to reappear at a slightly

deeper level. Since observations on ultrathin sections are strictly two-dimensional, it is not known whether such an obliteration occurred around the entire circumference of the vessel or represented only a localized occlusion of this space. Such a focal narrowing or actual obliteration of the perivascular space would result in a functional situation resembling that proposed by Schaltenbrand,[32] who believed that this kind of arrangement more or less hindered communication between the subarachnoid and perivascular spaces.

It is apparent from this study that the perivascular space terminates at the point where the glial and vascular basement membranes become confluent. If our conception of the perivascular space is correct and its existence depends only on the presence of mesenchymal elements (even a single adventitial cell process would seem to be sufficient) between the basement membranes of the glia and vessel, the concept of inner and outer reticular connective tissue sheaths derived from the arachnoid and pia, respectively, and constituting the boundaries of the space would seem to be both unnecessary and somewhat inaccurate. From the foregoing definition of the perivascular space, it follows and should be stressed that, at the capillary level, where there is no adventitia and the basement membranes of the vessel wall and brain tissue have merged, there is also no perivascular space.

The 2 most thorough and authoritative investigations in this area differ as to location of the artifactitious spaces of the brain. Patek[6] mentions 3 separate artificial compartments, and Woollam and Millen[8,31] describe 1 such space. It is, therefore, of some interest that, in our osmium-fixed and methacrylate-embedded material, similar mechanical artifacts could occasionally be demonstrated. With the high resolution of the electron microscope, these alterations could be exactly localized and identified as tears in the cytoplasm of the marginal astrocytes. It is probable that the artifact spaces often seen in many histologic preparations for light microscopy and usually termed the spaces of His or Held[6,8] also involve a tearing of the astrocytic processes in the same location.

SUMMARY

Normal and experimental pathologic specimens from the brains of Syrian hamsters were studied with the electron microscope with reference to the organization and relationships of the subarachnoid and perivascular spaces.

The brain surface is composed of astrocytic processes which are completely covered by a continuous basement membrane. Pial cells make up a unicellular sheet and, together with similar processes from the multilayered arachnoid, bound the subarachnoid space.

Arteries and veins possess a basement membrane enclosing elements of the tunica media and continuous with that of the endothelium. The marginal glia and their basement membrane follow and surround the penetrating vessels. The space lying between the glial basement membrane and the basement membrane of the vessel wall contains adventitial elements and is considered the "true" perivascular space. Plasma exudation within this space was seen in locally x-irradiated animals The glial and vascular basement membranes also serve to confine inflammatory cells and are the structural basis for the circumscribed perivascular "cuffing" in these animals with experimental cerebral infections. The true perivascular space terminates when the two basement membranes become confluent. At the capillary level, where adventitia is absent, the perivascular space is also nonexistent.

In occasional preparations, the marginal glia appeared torn, resulting in an artificial space similar to the artifactitious space of His or Held.

The authors express their appreciation to Professor Rollwagen of the II Physics Institute of the University of Munich for the use of his electron microscopic facilities. The technical assistance of Miss Luh and Mr. Fellner is also gratefully acknowledged.

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The electroencephalogram and performance in epileptic patients

H. F. R. Prechtl, Ph.D., P. E. Boeke, Ph.D., and T. Schut

IT IS AN ESTABLISHED FACT that epileptic patients show fluctuations in consciousness and reactivity. Numerous psychologic tests are based on this fact, for example, Kraepelin's calculation test and Bourdon-Wiersma's stipple test.

On the other hand, the electroencephalographer is familiar with paroxysmal changes in the bioelectrical activity of the epileptic patient's cerebrum. It is therefore an obvious suggestion that the changes in behavior are in some way correlated with epileptic activity as seen on the electroencephalogram.

The focus of our investigation was to study whether and how paroxysmal electroencephalographic patterns would correlate with fluctuations in behavior. For this purpose, it was necessary to devise a performance test which could be recorded simultaneously with the electroencephalogram.

METHOD

In order to insure simultaneous registration of a test performance and an electroencephalographic tracing, an apparatus had to be developed which would require the subject to carry out a continuous activity but which would not allow him to automatize his performance. The task had to be simple and yet had to include possibilities for making errors and for changes in the rate of performance.

After several attempts, we finally ordered an electronic apparatus which operated in the following way: Each of 5 small lamps is connected with a push button by which the lamp can be turned off; a special circuit controlled by a counting tube guarantees that only 1 lamp lights up at a time. Once the correct button is pushed and the lamp is extinguished, another lamp lights up immediately, according to a random order. The speed with which the counting tube randomizes the sequence of lights being turned on prevents any programming on the part of the subject.

The test subjects were instructed to extinguish each light as soon as it turned on by pushing the corresponding button with the right index finger and to proceed as rapidly as possible without making errors.

During the experiment, the subject was seated at a small table. The electroencephalographic electrodes were attached to the scalp in the usual manner; 1 channel of an 8-channel Grass A III apparatus registered the signal from the test apparatus, each button push giving 1 signal. The other 7 channels recorded from the scalp. A correct response to the light gave a signal on the electroencephalogram which could be clearly differentiated from the signals recorded when the subject pushed the wrong button.

Only after the subjects had been instructed about the test and after a continuous electroencephalographic pretest recording had been run for several minutes did the actual testing period begin. Any single test lasted for at least three minutes, and, after a certain interval of rest, the test was repeated in the same manner. The results were analyzed as follows: The distances between test signals (push button intervals = PIs) were measured independent of the electroencephalographic tracing; the tracing was studied independent of the performance signals, and changes in electrical activity

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which were thought to be significant were marked on the tracing. Only then were the electroencephalographic patterns and the PIs compared and the correlations statistically evaluated.

The investigation was carried out on 10 normal adults (5 men and 5 women) and 12 adult patients with clinical symptoms of epilepsy (7 men and 5 women); 1 or several routine electroencephalograms were made in all cases. A description of clinical symptoms and electroencephalographic findings is presented in Table 1.

RESULTS

Data analysis of the first few subjects clearly showed that there is no simple temporal correlation between epileptic activity in the electroencephalogram and the rate of performance on the test. For example, 1 patient made no errors and performed at his usual rate even during ten seconds of generalized spike and wave activity. In other patients, when the electroencephalogram showed focal spike or sharp wave activity, in general there was also no change of test performance. However, changes in performance rate were frequently associated with a very flat, undifferentiated wave pattern, often unrelated to but sometimes followed by unmistakable epileptic discharges. We then compared the PIs of epileptic patients during periods when the electroencephalogram showed no marked changes for long periods of time and those during periods when the electroencephalogram showed suppression and epileptic discharges as described above. In each of the 10 patients examined, the PIs during normal electroencephalographic activity were different from those during suppression. This difference was evident both with respect to the average value of the PIs and the irregularity of the performance rate. In Figure

TABLE 1
CLINICAL SYMPTOMS AND ELECTROENCEPHALOGRAPHIC FINDINGS IN 12 EPILEPTIC PATIENTS

Case No.	*Sex*	*Age*	*Clinical symptoms*	*Background activity in electroencephalogram*	*Type of epileptic discharge in electroencephalogram*
1	F	29	4 times commotio grand mal	Rather disturbed	Spikes and waves
2	M	43	Frequently absences and grand mal	Slowed	Spikes and waves
3	M	53	Grand mal	Undisturbed	Paroxysms of theta and alpha frequency
4	F	17	Psychomotor attacks	Undisturbed	Left temporal slow spike–slow wave focus
5	F	22	Psychomotor attacks and grand mal	Slowed	Theta paroxysms
6	M	37	Grand mal	Slowed	Without
7	M	55	Psychomotor attacks	Slowed	Bitemporal spike activity
8	M	15	Aggressive bursts	Slowed	Left temporal sharp wave focus
9	F	19	Grand mal	Slowed	Right frontoparietal sharp wave focus and diffuse spikes and waves
10	M	27	Akinetic seizures	Undisturbed	Theta paroxysms
11	M	20	Grand mal and absences	Slowed	Theta paroxysms
12	F	29	Visual aura and grand mal	Greatly disturbed	Frequently spikes diffuse in the left hemisphere

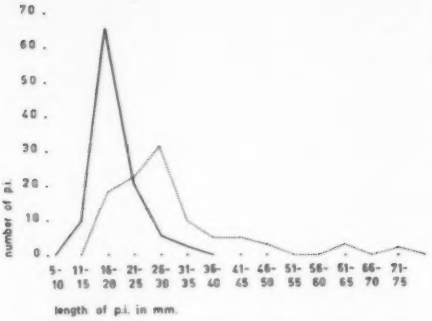

Fig. 1. Frequency distribution of interval duration (abscissa in millimeters). The continuous line shows the PIs in the normal parts of the electroencephalogram, while the dotted line shows those during suppression. Female with psychomotor attacks (aged 17)

1, this tendency is illustrated for 1 patient; the frequency of his PIs during normal and suppressed electroencephalographic periods is shown in graphs. Figure 2 gives the same for each of the 10 patients. Examples of suppression in the electroencephalogram are presented in Figures 3 and 4.

During periods of epileptic discharge, however, there were no distinct changes of performance. Comparing the normal periods of a patient with those during which spikes and waves were continuously seen, we found only a very slight difference (Fig. 5). The average values and standard deviations were almost congruent. However, a striking feature was that the same patient (Fig. 5) showed a significant irregularity in the rate of performance during the three seconds preceding each spike and wave attack; this irregularity was not observed following the spike and wave attack (Fig. 6).

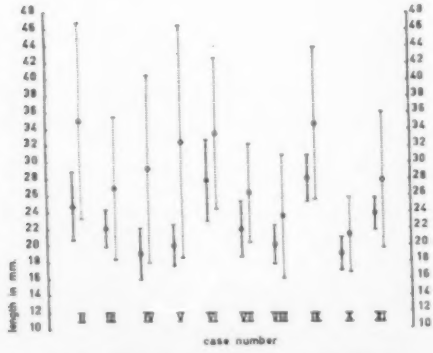

Fig. 2. Average values and standard deviations of normal and suppressed electroencephalographic periods in 10 epileptic patients. Continuous line = normal parts of the electroencephalogram. Dotted line = suppressions

Statistical analysis of the results obtained in the 10 patients (Fig. 2) shows the following: A comparison of the average PI values during normal periods and periods of electroencephalographic suppression revealed significant differences (chi-square test) in only 6 of the 10 patients. This means that only in those 6 was the test speed significantly decreased during the suppression. However, an investigation of the variance (sigma-square) of the PI (F test) showed a significant irregularity in working speed during suppression in each of the 10 patients. A detailed report of the findings is given in Table 2.

A comparison of these results with those obtained in 10 normal test subjects (Fig. 7) shows that both the average values and the variances of all PIs in the 2 groups are different. The average values of the epileptic patients are lower than those in the normal subjects (significance of $p = 0.01$ by Wilcoxon test). Using the same statistical analysis to test how the working speed of the 2 groups differed, we found that epileptic patients have a significantly greater irregularity than normal persons ($p = 0.01$).

An interesting result was obtained by comparing the total PIs in the normal group and in the patients during the normal electroencephalographic periods. The average values in the epileptic patients were again significantly lower ($p = 0.01$ by Wilcoxon test), probably due to the sedative effect of anticonvulsant medication, but there was no significant difference in the regularity of working speed as expressed by the analysis (sigma-square) of variance (Fig. 8). This means that, during normal electroencephalographic activity, epileptic patients perform more slowly than normal subjects, but their performance is not more irregular.

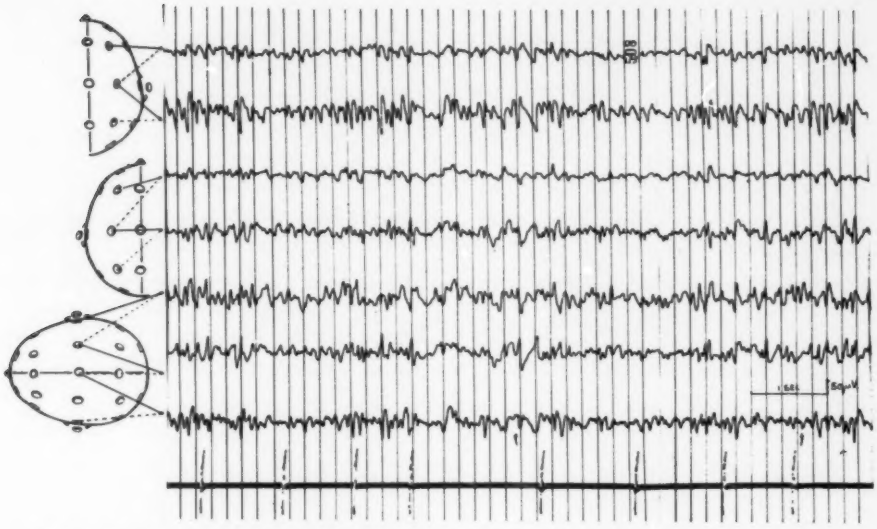

Fig. 3. Example of suppression of electrical activity and simultaneous deceleration of reactions. Bottom part = registration of signals from the test apparatus

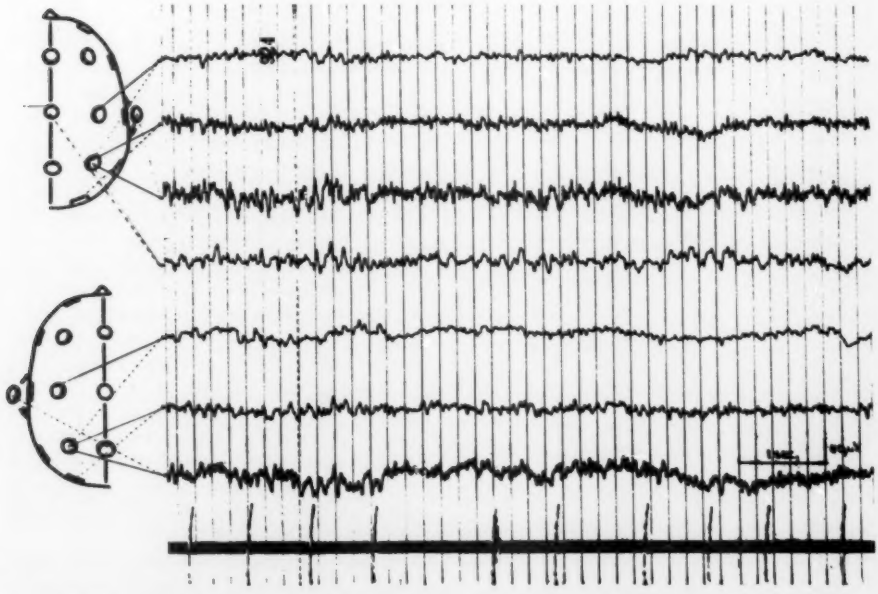

Fig. 4. Example of suppression of electrical activity and simultaneous deceleration of reactions. Bottom part = registration of signals from the test apparatus

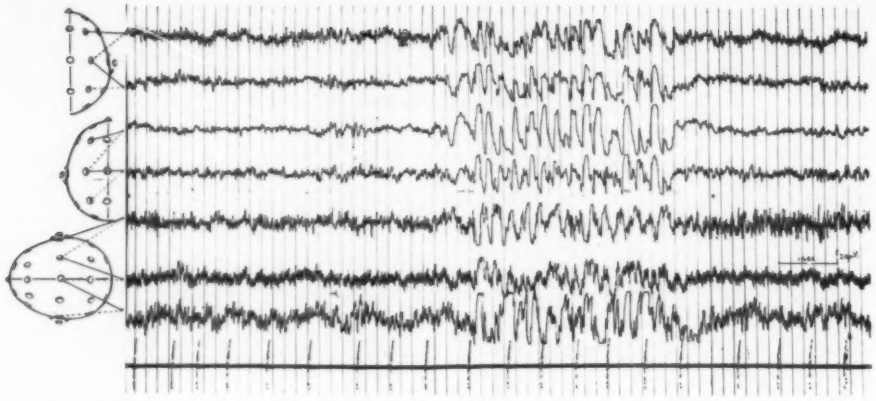

Fig. 5. Example of a spike and wave attack lasting four seconds; reactions continue undisturbed. Patient with grand mal seizures (aged 43)

DISCUSSION

The findings show that the changes in test performance are correlated with specific changes in electroencephalographic pattern. Surprisingly, however, in our cases, the impairment in performance does not correlate with a breakthrough of epileptic activity over large areas of the brain but rather with a suppression of the activity as visualized in the electroencephalogram. (The suppression effect was seen to influence also the background activity.) Electroencephalographic patterns of this kind were not encountered in nonepileptic subjects, in whom the deviation from the average PI value was very slight. The suppression is therefore not the result of arousal or vigilance in response to the test situation. Episodes of suppression may also be observed in the routine electroencephalograms of epileptic patients and then occur sometimes as isolated events, but often they are followed by a typical epileptic discharge. However, the routine electroencephalograms of epileptic patients and the electroencephalograms during the test situation did differ with respect to the frequency of epileptic discharges; these were generally lower during periods of concentrated attention and associated arousal than during routine procedures, when the patient is relaxed and shows alpha-waves.

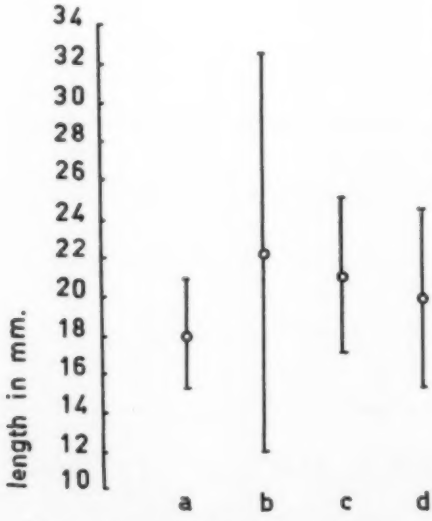

Fig. 6. Average values and standard deviations of PIs in a female patient with spike and wave episodes (grand mal, aged 29). [a] Normal electroencephalogram; [b] three seconds before spike and wave episode; [c] during episode; [d] three seconds afterward.

Penfield and Jasper[1] have described similar episodes of suppression of electrical activity in several epileptic patients, chiefly as the result of electrical stimulation of the rhinencephalon

(periamygdaloid region, anterior insula, or cingular region). "Not only are normal rhythms arrested, but even spontaneous epileptiform discharge may be stopped for a time. Suppression occurs over large areas at a distance from the site of stimulation" (p. 728). The suppression is sometimes the sole sequela of a stimulation; in other cases, however, there is also an outbreak of spikes. In some patients, attacks start with suppression of electrical activity in the electroencephalogram.

The above considerations warrant the conclusion that the suppression seen in the electroencephalograms of epileptic patients constitutes a manifestation of subcortical epileptic discharges, although the pathophysiologic mechanisms can at present only be guessed at.

Our results show that, in terms of behavior, this suppression in the electroencephalogram is associated with an arrest of performance. It is impossible to state whether the disturbance is localized in the sensory or the motor cortex or in both; nor can it be decided whether and to what extent the change can be described as a change of consciousness.

A practical aspect of these findings would seem to be the fact that epileptic patients whose electroencephalograms no longer show epileptic discharges after anticonvulsant ther-

TABLE 2

COMPARISON OF DIFFERENCES IN AVERAGE VALUE AND VARIANCE (WILCOXON TEST) OF BUTTON PUSH INTERVALS DURING NORMAL AND SUPPRESSED TRACINGS IN EPILEPTIC PATIENTS

Average value				
Significance	p=0.01	p=0.02	p=0.05	No significance
Number of patients	5	1	–	4
Variance				
Significance	p=0.01	p=0.02	p=0.05	No significance
Number of patients	9	–	1	–

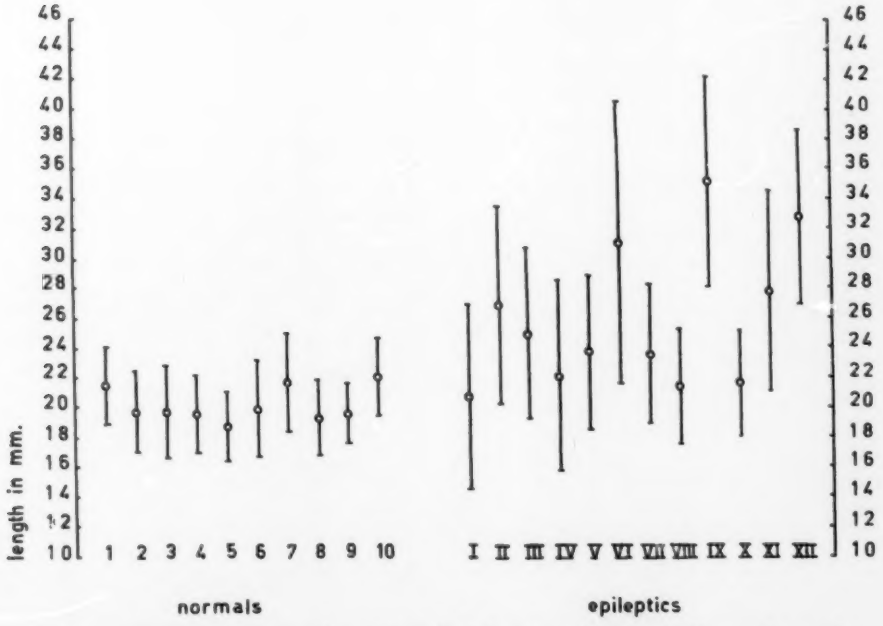

Fig. 7. Comparison of average values and standard deviations of all PIs in 10 normal test subjects and 12 epileptic patients

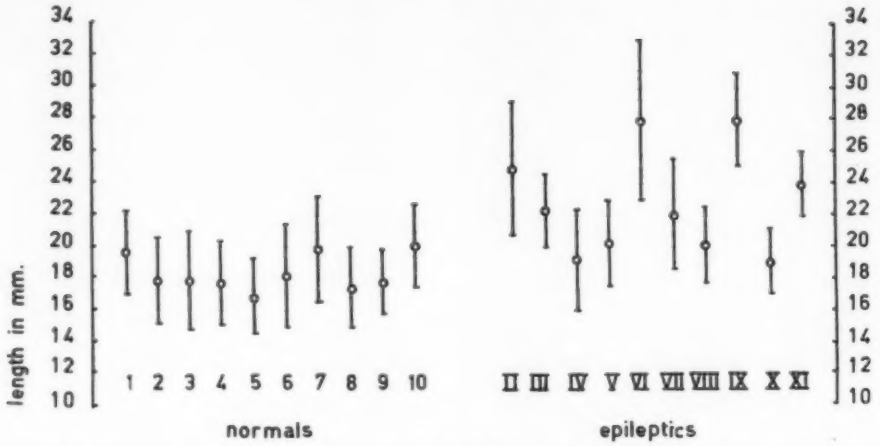

Fig. 8. Comparison of average values and standard deviations in PIs in 10 normal test subjects with the PIs during normal electroencephalographic periods in epileptic patients

apy but do show episodes of suppression may still be subject to considerable fluctuations in performance, for example, impaired reaction time at work or while driving a car. This aspect may so far have received insufficient attention in the routine interpretation of the electroencephalogram.

SUMMARY

The electroencephalograms of 10 normal subjects and 12 epileptic patients (grand mal and psychomotor attacks) were recorded together with a continuous performance test. For this test, an electronic apparatus was devised in which each of 5 small lamps could be turned off by pushing a button corresponding to the light. Only 1 lamp at a time turned on, and the task was to push the correct button to turn off the lamp as quickly and accurately as possible. As soon as 1 lamp was extinguished, another turned on automatically in random order. The correct or incorrect performances were automatically marked on the electroencephalographic tracings, and the intervals between responses to the light were measured, compared with the electroencephalographic pattern, and statistically evaluated.

In general, the rate of performance was unchanged during epileptic discharges (focal spikes or spike and wave patterns). However, the mean and the variance of the interval between correct performances in pushing the button were significantly higher during paroxysmal and diffuse flattening of the electrical activity of the brain (suppression) than during normal electroencephalographic activity ($p = <0.01$). The theoretic and practical consequences of these findings were discussed.

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Familial tumors of the "glomus jugulare"

Report of 2 cases, with a note on the vascular origin of the glomera

Jules C. Ladenheim, M.D., and Ernest Sachs, Jr., M.D.

SMALL MASSES OF vascular tissue histologically resembling the carotid body have been described in the vicinity of the middle ear by Valentin,[1] Krause,[2] and Watzka.[3] Guild[4] revived interest in these bodies and assigned to them the collective term "glomus jugularis." Later, for grammatical considerations,[5] the name was changed to "glomus jugulare." The histologic structure of the glomus jugulare was found to consist of "blood vessels of capillary and precapillary caliber with numerous epithelioid cells between the vessels."[6] In accordance with carotid body concepts, Guild regarded these glomera as "paraganglia" and, accordingly, related their distribution to the nerves of Jacobson and Arnold (auricular branch of the vagus), as well as to the antrum of the jugular vein in proximity to the jugular ganglion.

Even before the publication of Guild's paper, however, impressive evidence indicated that the carotid body is *not* a paraganglion but a vascular structure surrounded by a mesenchymal condensation, *deriving* whatever paraganglion cells it may exhibit in a given specimen from the adjacent cranial nerves or sympathetic chain.[7,8] Thus, the discrepancies reported by different authors in the proportion of the chromaffin and nonchromaffin cells found in the glomus are reconcilable, since the migration to the glomus of paraganglion cells from the investing nervous tissue is determined to some extent by chance.

In 1935, Ask-Upmark[9] studied the evolution of the rete mirabile (wonderful net). This structure, related to the pseudobranch of fish, is composed of a network of small arterial vessels having an afferent artery derived from the external carotid artery and an efferent artery which supplies the proximal regions of the eustachian tube. The larger arteries of the rete mirabile are elastic and have strong longitudinal bundles of muscle fibers which form cushion-like invaginations capable of obliterating the lumen. Smaller arteries have sphincter-muscle regulatory mechanisms for blood flow. Although not a prominent part of the anatomic structure, arteriovenous connections are also present.[10] The function of the rete mirabile is not entirely clear, but Ask-Upmark speculated that they contribute to the hydrodynamic control of blood pressure, and, thus, despite the differences in anatomic structure, the rete mirabile may perform in lower forms a function similar to that of the carotid sinus in primates.[9]

Since many of the basic features of the rete mirabile are encountered in the glomus jugulare, these two structures have been regarded as homologues.[11] This concept further postulates that the glomera take their origin from the external carotid-stapedial arterial system of the second visceral arch during the period when the vessels are surrounded by cranial nerve structures. *With the subsequent regression of the branches of the stapedial system,[12] the vascular origin of these glomera has become obscured, and the erroneous impression thereby engendered that they have arisen from the neighboring cranial nerves, especially from branches of the glossopharyngeal and vagus nerves.* The term "glomus jugulare" then, evolving from a mistaken concept, anatomically fails to describe structures situated apart

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from the region of the jugular antrum. Since the vascular origin proposed by Ask-Upmark[11] accounts for the occurrences beyond the jugular bulb in the distribution observed by Guild,[6] these bodies should be regarded as glomera of the external carotid artery. Unfortunately, usage impedes the alteration of a name.

Although several middle ear glomangiomas have been reported in the literature under a variety of titles, such as perithelioma, hemangioma, endothelioma, and so forth,[13,14] Lubbers[15] appears to have been the first to relate the tumor to the glomera. Published as an abstract in a Dutch Journal in 1937, his communication attracted scant attention until the report of similar observations by Rosenwasser.[16] Since then, about 200 cases have appeared in the literature, to extrapolate from a recent census.[14]

Several instances of *familial* glomeral tumors of the middle ear region have been recorded. Goekoop[17] reported middle ear "fibro-haemangioma" occurring in 3 sisters. Another series of 3 sisters who probably had tumors of the glomus jugulare was presented by Wassink.[18] Bartels[19] traced a family in which, during 3 generations, 7 members developed a tumor of the glomus jugulare, carotid body, or both. Linn and Proctor[20] described a familial tumor in 2 female siblings, 1 of whom had a carotid tumor and a vagus tumor, the other a glomus tumor of the middle ear region.

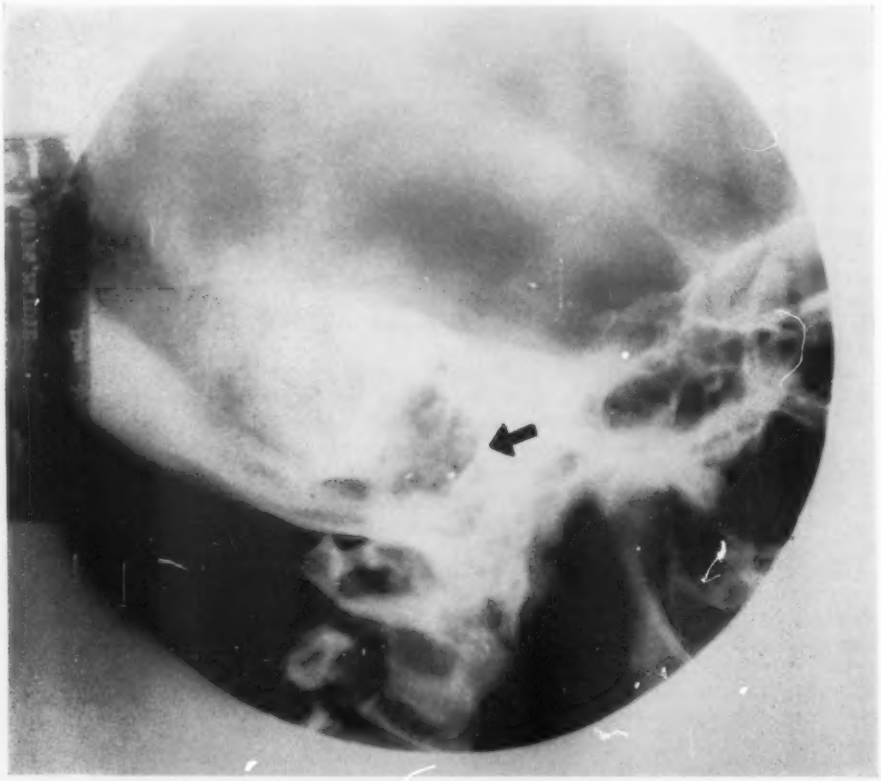

Fig. 1. Right lateral skull roentgenogram. An osseous defect is present in the region of the right auditory meatus, extending toward the tip of the mastoid *(Case 1)*.

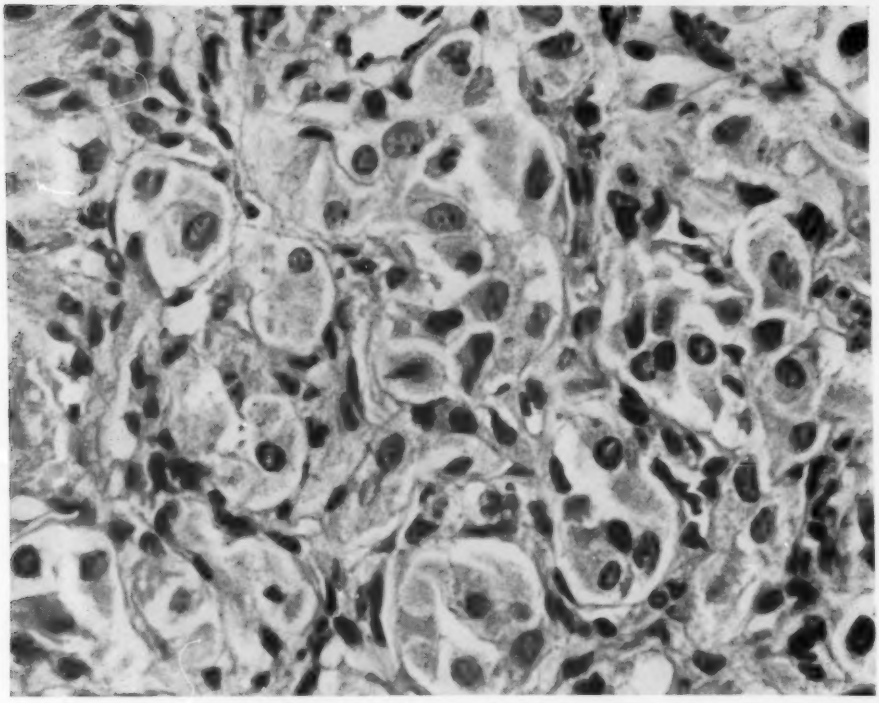

Fig. 2. Small nests of epithelioid cells are separated by delicate connective tissue septa *(Case 1)*. Hematoxylin and eosin. × 1,200

CASE REPORTS

Case 1. M. G., a 29-year-old woman, was referred to the Hitchcock Clinic on February 10, 1951, because of right ear pain and severe headaches of about six months' duration. Roentgenograms made at another hospital had demonstrated destruction in the lower pole of the right mastoid bone.

Examination. Slight mental retardation was noted. A bruit was heard over the right mastoid region which could be reduced but not obliterated by compression of the right common carotid artery. An eroding vascular tumor was present in the floor of the right auditory canal.

Audiography disclosed a marked decrease in hearing on the right side. Skull roentgenograms (Fig. 1) showed a well-defined osseous defect from the auditory meatus to the mastoid tip. The petrous ridges and internal auditory meatus, however, had a normal radiographic appearance. Right internal and external carotid arteriography failed to show any unusual vascularity in the area of the erosion. Biopsy of the external canal tumor revealed typical glomus jugular tumor (Fig. 2).

Operation. Under general anesthesia, ligation of the external carotid artery was performed on February 19, 1951.

Course. Following ligation, great reduction in the intensity of the bruit was noted, but the bruit was not totally abolished. A course of 2,400 r radiation was administered to the tumor area.

In December 1956, the patient began to have headaches, dizziness, and slight facial hypesthesia, which corresponded to the first and second divisions of the left (contralateral) trigeminal nerve. There was no x-ray evidence of a left-sided skull lesion. Another course of 2,400 r was administered to the *right* side because the bruit on the right, headaches, and dizziness persisted. Since then, the patient has had no further neurologic complaints nor have any additional signs appeared. She was last seen at the Hitchcock Clinic in October 1959, at which time she stated that she could still occasionally hear the bruit. She has worked daily since 1951. A recent communication from another hospital advises that she underwent successful radiotherapy for epidermoid carcinoma of the cervix.

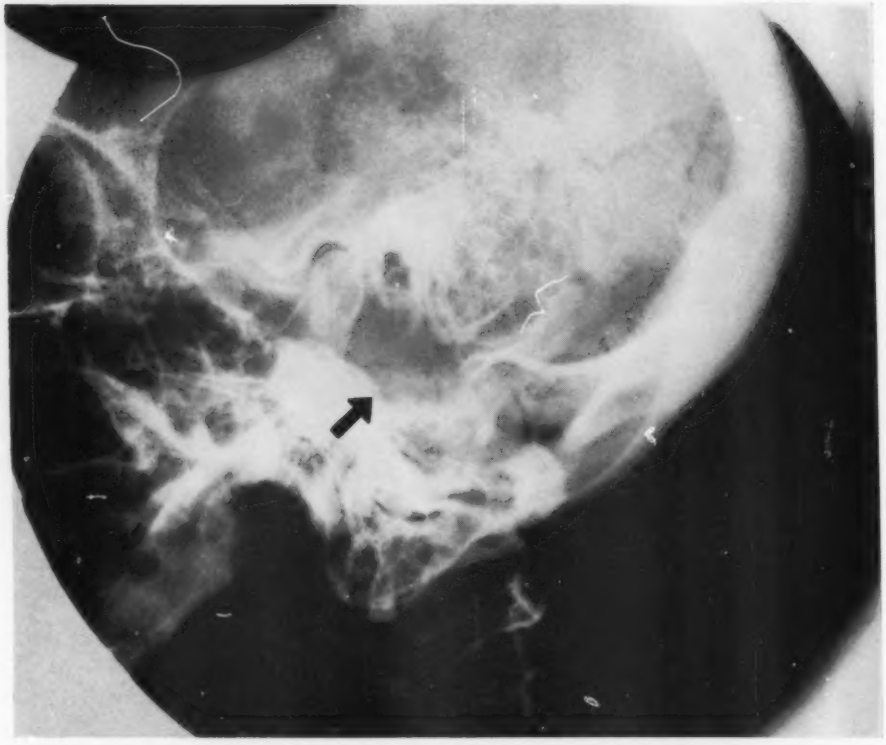

Fig. 3. Left lateral skull roentgenogram. Extensive destruction of left petrous ridge *(Case 2)*

Case 2. A. S., a 29-year-old married woman, a sister of the previous patient, was referred to the Hitchcock Clinic on June 6, 1955, because of pain and bleeding from a large mass filling the left external canal. The patient was somewhat retarded mentally and could not give a good history. Four years previously, she suddenly experienced hoarseness which had persisted. Two or three months later, diplopia appeared. Very shortly thereafter, a left facial palsy was noted and had persisted. In the intervening years, deafness of the left ear and balance changes appeared. Eleven months before admission, at age 28, the patient ceased to menstruate. Five months before admission, bleeding from the left ear occurred, and, for the past two to three months, she had been troubled by soft, inconstant noises in the left ear.

Examination. The left carotid artery felt larger than the right. A soft bruit was heard over the left side of the head, especially pronounced over the mastoid prominance. There were paralyses of the left V, VI, VII, VIII, IX, X, XI, XII cranial nerves. There were nystagmus and ataxia.

Skull roentgenograms disclosed extensive destruction of the left petrous ridge medial to the middle ear. This destruction involved the posterior portion of the sella turcica and appeared to extend into the sphenoid sinus, indicating involvement of the posterior and middle fossae (Fig. 3). Biopsy of the lesion in the ear was performed, and glomus jugulare tumor was diagnosed. Carotid arteriography revealed a large area (3 cm. in diameter) of "capillary blush" overlying the posterior portion of the sphenoid bone extending posteriorly, with venous drainage into the jugular vein.

Course. X-ray therapy of 2,400 r was administered to the lesion without arrest of symptoms. Dizziness continued and she was unable to perform her housework.

Second hospitalization. Three months later, the patient was readmitted. The cranial nerve palsies were unchanged, and, although she did not have papilledema, the ataxia had increased.

Operation. On October 20, 1955, under general anesthesia with hypothermia and artificially induced hypotension, preliminary ligation of the left

external carotid artery and occlusion of the left common carotid artery with a Selverstone clamp were done. Posterior fossa craniectomy was performed, and a large tumor extending from the left cerebellopontile angle to the middle fossa was exposed. The lateral sinus was ligated to promote further access to the tumor. The lesion could be partially extirpated, but, because of excessive bleeding from tumor, bone, and dura, complete removal could not be accomplished.

The sections revealed typical glomus jugulare tumor (Fig. 4).

Postoperative course. The patient regained consciousness after the operation and could move all extremities. Two days later, she became unresponsive and exhibited right hemiplegia and aphasia. The Selverstone clamp was released. The posterior fossa craniectomy was reexplored, disclosing cerebral edema without operative hematoma. The patient died forty-eight hours after the initial surgical procedure. Autopsy revealed a large tumor (150 gm.) in the left cerebellopontile angle, with erosion of half of the petrous pyramid and one-half of the clivus, the sella, the cavernous sinus, and the pterygopalatine fossa.

DISCUSSION

Symptoms deriving from the glomus tumors in the region of the middle ear appear chiefly in the fifth to seventh decades of life. Three-fourths of the patients are women.[21] Expanding laterally through the tympanic membrane, the lesion appears in the external auditory canal where it may be mistaken for a polyp. In this location, complaints of itching, bluish discharge,[22] or hemorrhage may be encountered. The tumor may expand upward through the petrous portion of the temporal bone to involve the third to sixth cranial nerves, inferiorly into the occipital bone, or into the posterior cranial fossa to invade the eighth to twelfth cranial nerves (Case 2). Invasion of

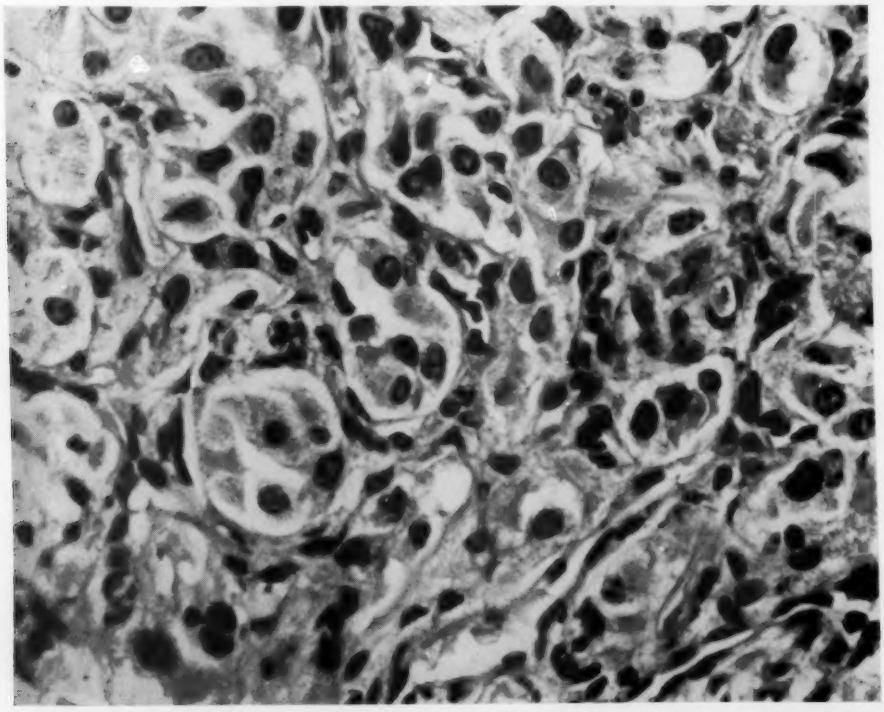

Fig. 4. Well-vascularized connective tissue stroma which separate numerous nests and cords of epithelial-like cells *(Case 2)*. Hematoxylin and eosin. × 1,200

the mastoid region may cause facial palsy.[23] Penetration of the dura has been reported.[13] In general, about 40% of the tumors are attended by evidence of intracranial extension.[24] Although middle ear symptoms usually attract clinical attention, neurologic symptoms have been known to initiate the clinical manifestations,[25] especially if the lesion arises near the jugular ganglion and early invades the posterior fossa.[23] If a bruit is present, it can be reduced or abolished by carotid artery compression.

The glomus tumor appears red or blue when seen through the tympanic membrane.[22] On microscopic examination, hyperplasia or neoplasia of the epithelioid cells destroys the normal arterial ramification and results in the formation of pathologic arteriovenous fistulas. These are responsible for the bruit and, in general, conform to the laws governing arteriovenous hemodynamics.[26] Of these tumors, 10% are said to be associated with other glomangiomas elsewhere in the body,[25] and the tumors occasionally occur bilaterally.[27] On rare occasions, malignant evolution and metastasis have been recorded.[6]

For the diagnosis of tumors appearing in the external auditory canal, the so-called "pulsation test" has been used.[28] Increasing pressure delivered through a tightly fitted external canal speculum causes the tumor to pulsate, and, as pressure is further increased, the tumor blanches. On one occasion, when a patient complained of a bruit which could not be heard by usual auscultation, we were able to hear the murmur with the following method: a stethoscope was placed in the ears of the patient and the diaphragm of that instrument was placed against a diaphragm of a stethoscope worn by the examiner. Caloric stimulation discloses the reduction or absence of the homolateral labyrinth response.[22] Audiometric examination usually reveals profound hearing loss.[29] When the tumor has penetrated the tympanic membrane, the diagnosis can, of course, be made by biopsy. Skull roentgenograms may reveal sclerosis or clouding of the mastoid, destruction of the petrous ridge, destruction of the skull base, or widening of the internal auditory meatus, dependent on the mode of growth of the tumor.[23] Although the blood supply of the glomus tumor is derived from the ascending pharyngeal branch of the external carotid artery, the tumor does not often appear during carotid angiography, notwithstanding the presence of arteriovenous fistulas and a bruit. Perhaps this is because, among other reasons, the mastoid shadows obscure visualization.[30] Dilated vessels, however, can sometimes be seen in the phlebographic phase.[31]

Several methods of treatment have been formulated, reflecting the variants of growth of the tumor and the proclivities of the physician. In general, small tumors should be removed surgically,[22] but, since the presenting lesion is frequently of considerable size, obscuring the normal anatomic landmarks,[32] the risks attending complete removal by radical surgery are often disproportionate to the derivative benefits. As with most arteriovenous formations, ligation of the afferent artery, that is, the external carotid artery, is usually not spectacularly successful, and, for this reason, recourse had to be made to radiation in the treatment of the Case 1. Radiation in large doses has been successfully employed by some authors,[33,34] while others have removed portions[28] or all[35] of the tumor infiltrating the middle or posterior cranial fossae. Lastly, when the tumor growth is slow and the symptoms of the patient minor, the lesion might be left undisturbed.

SUMMARY

The theories relating to the origin of the glomera found in the region of the middle ear are reviewed.

Two cases of glomus tumors occurring in sisters are presented.

A method for eliciting bruit when not heard by the usual method of auscultation is offered. A bruit is believed to arise from the conversion of a normal precapillary vascular ramification to pathologic arteriovenous fistulas following neoplasia or hyperplasia of the epithelioid cells. Because of the opportunities for collateral blood supply to the tumor, ligation of the afferent artery (external carotid) is usually not effective therapy.

The indications for radiation, extirpation, and *laissez faire* as possible modes of therapy for the glomus tumor are evaluated and discussed.

CONCLUSIONS

Glomera in the middle ear region are retrogressive homologues of the rete mirabile. The terms "glomus of the middle ear region" (descriptive) or "glomus of the external carotid artery" (anatomic) are more proper embryologically than glomus jugulare. Since tumors of these structures are often multiple and sometimes familial, complete examination of the patient and the family, especially female members, will at times disclose asymptomatic tumors. No single ideal form of therapy has yet been devised.

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Intracranial hemorrhage in patients with bleeding tendencies

Allen Silverstein, M.D.

THE PERFORMANCE of early cerebral arteriography (and possibly craniotomy) in patients with subarachnoid and other forms of intracranial hemorrhage has gained many advocates in recent years. However, intracranial bleeding may occasionally be the presenting manifestation of a coagulation defect; if arteriography and craniotomy are undertaken before recognition and attempted correction of this defect, disastrous complications may result.

The occurrence of intracranial hemorrhage in patients with known bleeding tendencies is more common. Intracranial bleeding in these patients has usually been considered fatal, and adequate neurologic investigation has been performed only rarely. This may well be unfortunate, since the life of an occasional patient with a hemorrhagic diathesis and bleeding confined to an accessible site may be saved by proper study and intervention.

Few statistical data have been accumulated concerning the frequency, site, and clinical and pathologic features of intracranial hemorrhage in patients with bleeding tendencies. Furthermore, review of the literature has revealed almost no recent writings concerning the management of such hemorrhage. The Hematology, Neurology, and Neuropathology records and files of the Mount Sinai Hospital from 1952 through 1958 have been reviewed for purposes of this communication. Analysis of occurrence of intracranial hemorrhage in patients with bleeding tendencies during this seven-year period is the substance of this report.

MATERIALS AND METHODS

Only patients in whom both intracranial hemorrhage and a bleeding tendency could be proved were included in this study. The cause of death in many patients with bleeding tendencies who were observed during the period under review was ascribed to intracranial hemorrhage. However, in several of these patients, subsequent autopsy failed to reveal any bleeding within or around the brain. Because of this, one of the following has been required for proof of intracranial bleeding: [1] presence of intracranial hemorrhage as determined by autopsy or craniotomy; [2] aspiration of nontraumatic bloody fluid from the subdural space in infants; and [3] presence of nontraumatic bloody cerebrospinal fluid obtained by lumbar puncture in patients with intracranial signs and symptoms.

A bleeding tendency was considered proved if one or more of the coagulation tests listed in Table 1 was found to be abnormal. Diagnosis of the hematologic disease in each patient was based upon the current classification and criteria of the Department of Hematology of the Mount Sinai Hospital.

RESULTS

Intracranial bleeding and a hemorrhagic diathesis were proved in 58 patients during the seven-year period under review; 30 were males, and 28 were females. Their ages ranged from newborn to 78 years. The bleeding tendency was known for some time (up to forty

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TABLE 1
PROCEDURES USED IN THE PRESENT STUDY FOR EVALUATING COAGULATION

1. Rumpel-Leede (tourniquet) test
2. Bleeding time (Ivy)
3. Clotting time (Lee-White modified technic)
4. Platelet count (direct method)
5. One-stage prothrombin time (Quick)
6. Two-stage prothrombin time (Owren)
7. Tests for labile factor (proaccelerin, factor V) and stable factor (proconvertin, serum prothrombin conversion accelerator, factor VII) (Owren)
8. Fibrinogen level (biuret method)
9. Serum prothrombin activity
10. Thromboplastin generation test (Biggs and Douglas)
11. Hemophilia screening tests
12. Fibrinolysin detection

years) before the intracranial episode in most patients; in 4, however, intracranial signs and symptoms preceded the recognition of a coagulation defect.

Hematologic data. Thrombocytopenia was by far the most common coagulation defect associated with intracranial bleeding and was found in 51 patients in this series. The diseases responsible for the thrombocytopenia were as follows:

	Number of Patients
Acute blastic leukemia	16
Subacute or chronic myelogenous leukemia	11
Aplastic anemia	7
Myeloproliferative disease	4
Neonatal thrombocytopenia	3
"Idiopathic" thrombocytopenia	3
Thrombotic thrombocytopenia	3
Reticulum cell sarcoma	2
Chronic lymphatic leukemia	1
Hemangioendothelial sarcomatosis	1

Hypoprothrombinemia was present in 3 patients. Dicumarol toxicity was responsible in 2, while the third patient had severe hepatic disease. The remaining 4 patients, all with hemophilia, have been reported elsewhere.[1] In addition to thrombocytopenia, hypofibrinogenemia was observed in at least 3 of the patients with leukemia.

Evidence of bleeding other than intracranial was noted in 56 patients. Skin petechiae or purpura was noted in 49, 28 had upper and lower gastrointestinal bleeding, and 20 experienced genitourinary bleeding. Epistaxis occurred in 18 patients, and there were hemorrhages in the palate or pharynx of 10, gingiva of 9, and conjunctiva of 3.

The incidence of intracranial hemorrhage in patients admitted with thrombocytopenias of various etiologies during the seven-year period under review is presented in Table 2.

Neurologic data. A history of prior head trauma was obtained in only 4 patients. Severe headaches occurred in 15 patients, and convulsions of one form or another were reported in 11. There were scanty neurologic symptoms in 9 patients, and only 3 had lateralizing symptoms such as hemiparesis; 20 patients died within twenty-four hours after onset of neurologic symptoms. This rapid exitus occurred predominantly in patients with acute leukemia.

The neurologic signs observed in the present series varied with the site of intracranial bleeding and generally did not differ from signs of intracranial bleeding in patients without coagulation defects. Thus, disturbances of consciousness occurred in 37 patients, anisocoria was noted in 11, meningeal signs were found in 9, and 8 had focal findings such as hemiparesis or homonymous visual field defects. Hemorrhages were observed in the fundi of 20 patients, while papilledema was noted in only 6.

Lumbar punctures were performed 49 times in 21 patients. The cerebrospinal fluid was abnormal in all patients. In 12, there was bloody

TABLE 2
PROVED INTRACRANIAL BLEEDING IN PATIENTS ADMITTED WITH VARIOUS HEMATOLOGIC DISEASES, 1952-1958

Diseases	*Number of patients admitted*	*Number with proved intracranial hemorrhage*	*Incidence*
Leukemia (excluding chronic lymphatic)	361	27	7.1%
Aplastic anemia	46	7	15.2%
Myeloproliferative disorders	120	4	3.3%
Other thrombocytopenias	364	13	3.6%

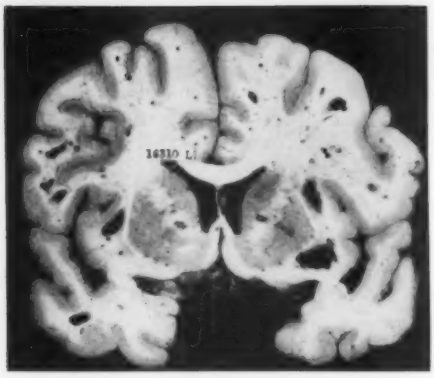

Fig. 1. Multiple small focal hemorrhages in the brain of a 5-year-old child dying from acute blastic leukemia. Platelet count before death was 8,000. Neurologic signs appeared twenty-four hours before death with acute onset of coma.

fluid; xanthochromic fluid was obtained from 6, and clear fluid under increased pressure or with an elevated protein was present in 2. Bacterial meningitis was diagnosed by lumbar puncture in 1 patient, who was found to have intracerebral bleeding at subsequent autopsy. Subdural aspirations were performed 4 times in 2 infants, and bloody fluid was obtained once. No noteworthy complications followed any of the 49 lumbar punctures or 4 subdural aspirations performed in this series.

Carotid arteriograms and pneumoencephalograms were each performed 3 times. All studies were abnormal, and 2 subdural hematomas were shown by arteriography. A myelogram was performed in a leukemic patient with a severe radicular syndrome, who subsequently died from intracranial bleeding.

Craniotomy was undertaken in 7 patients. Subdural hematomas were encountered in 2 and intracerebral hematomas in 3; 2 patients died the same day as surgery, and 2 died twenty-four and thirty-six hours after surgery, respectively.

Pathologic data. Intracranial bleeding occurred within the brain in 43 patients. Multiple small petechial hemorrhages were noted in 17 brains (Fig. 1). Relatively large hemorrhages (over 2 cm. in any diameter) were found in the cerebrum of 22 patients (Fig. 2), in the cerebellum of 3 (Fig. 3), and in the brain stem of 1. Only 8 of these large cerebral hemorrhages were solitary; the remainder were associated with petechial hemorrhages elsewhere. These small hemorrhages tended to occur perivascularly, especially in the leukemic patients. Actual leukemic infiltrates in the brain adjacent to these hemorrhages were observed microspically in 9 patients.

Bleeding primarily in the subarachnoid space occurred in 9 patients, while 6 had hemorrhage confined to the subdural compartment. Of the 43 patients with intracerebral bleeding, 15 had extension to the ventricular system (Fig. 4).

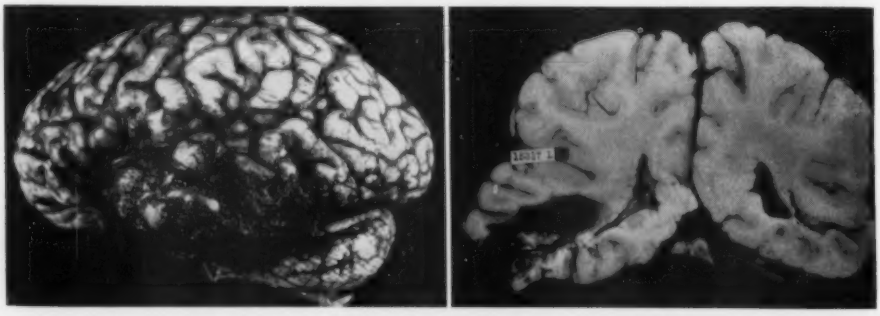

Fig. 2. Hemorrhage in the left temporal lobe extending to the subarachnoid space in a 45-year-old patient with severe aplastic anemia. Platelet count was 2,000. Onset of confusion and restlessness was gradual several days before death. Anisocoria, bilateral extensor plantar responses, and retinal hemorrhages were noted. Lumbar puncture revealed grossly bloody fluid.

Cingulate or uncinate herniations were noted in 4 patients. Symmetric lateral and midline brain stem hemorrhages—as are commonly seen with elevated supratentorial pressure—without multiple hemorrhages elsewhere were noted in 2 patients.

Correlative data. Few correlations could be drawn between the clinical and neuropathologic findings and the hematologic disease. In general, those diseases with thrombocytopenia produced similar multiple hemorrhages in the brain. These hemorrhages were somewhat more extensive and more closely related to blood vessels in patients with acute leukemia. The clinical course in acute leukemia seemed shorter, and death more rapidly followed the onset of neurologic symptoms in leukemic patients. The majority of patients with fundoscopic changes also had leukemia.

The sites of major intracranial bleeding with the various hematologic diseases are shown in Table 3. Patients with aplastic anemia tended to bleed more often into the subarachnoid space. This occurred in 3 of the 7 patients with aplastic anemia in this series. The 2 patients with Dicumarol toxicity both had subdural hematomas and have been reported elsewhere.[2]

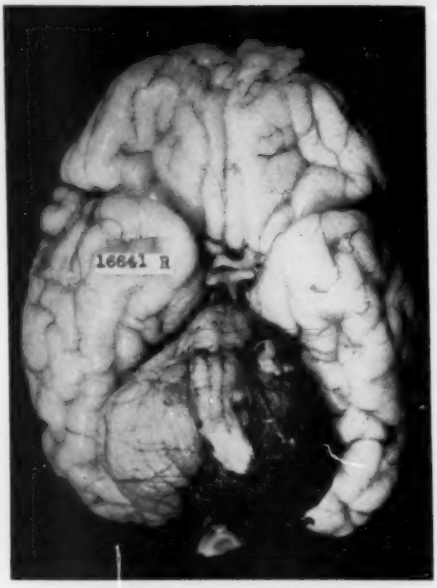

Fig. 3. Left cerebellar hemorrhage in a 19-day-old infant with neonatal thrombocytopenia. Platelet count was 25,000. The infant fed poorly from birth and had an absent Moro and later an absent sucking reflex.

DISCUSSION

That intracranial bleeding occurs most often with those hematologic diseases associated with thrombocytopenia has been suggested before.[3,4] The reported incidence of intracranial hemorrhage with thrombocytopenic purpura varies from 2.6[5] to 23%.[6] Many case reports have appeared, and the early literature has been reviewed adequately by Alpers and Duane.[7] Several patients with intracranial bleeding as the initial manifestation of their thrombocytopenia have been reported.[7–9] The most recently reported case is of interest in that the probable source of bleeding—an intracranial aneurysm—was demonstrated angiographically.[9]

It is said that such common symptoms as mild headache or dizziness in patients with thrombocytopenia represent "oozing" into the brain.[10] However, since such symptoms are also quite common in patients without bleeding tendencies, this conclusion may not necessarily be valid.

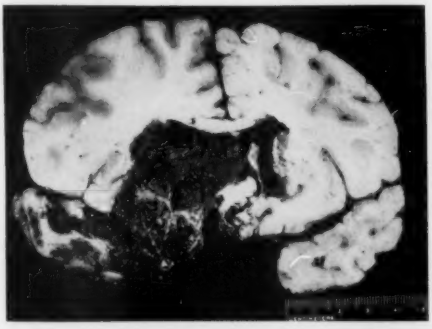

Fig. 4. Left cerebral hemorrhage extending into the ventricle and subarachnoid space in a 65-year-old patient with a myeloproliferative syndrome. Platelet count was 24,000. The neurologic illness began with a sudden convulsion, which was followed by persistent aphasia and right hemiparesis. Cerebrospinal fluid was heavily xanthochromic. Death occurred forty-eight hours later.

The diagnosis of intracranial bleeding must not be made in all patients with thrombocytopenia and cerebral signs and symptoms without further study. The characteristics of 2 specific diseases include thrombocytopenia and neurologic manifestations not necessarily due to intracranial bleeding. These diseases are disseminated lupus erythematosus and thrombotic thrombocytopenic purpura.

In this study, as shown in Table 2, patients with aplastic anemia bled intracranially more often than patients with thrombocytopenia of other etiologies. The incidences of intracranial hemorrhage in patients with aplastic anemia have varied in the literature from 8[11] to 26 per cent.[12]

Leukemia. Many reviews of the neurologic manifestations[13–23] and neuropathologic changes[24–29] associated with the various leukemias have been published. The reported incidence of clinical involvement of the nervous system with all types of leukemia varies from 8.6[25] to 22.5%,[15] with an incidence of 42.9%[21] reported for acute leukemia. Pathologic changes may be observed in the brains of as many as 83% of randomly selected patients with leukemia.[26] Intracranial hemorrhage is probably the most common and certainly the most serious of the various neurologic manifestations of leukemia. The incidences of intracranial hemorrhage in all forms of leukemia have recently been reported as low as 7.5%[23] and as high as 49%.[30]

The common and severe intracranial bleeding noted in patients with leukemia may be due to several factors. Unlike other hematologic diseases, multiple coagulation defects may be operating simultaneously. Thus, hypofibrinogenemia, fibrinolysin production, circulating "heparin-like" anticoagulants, and other deficiences, as well as thrombocytopenia, have been documented in leukemia.[30,31] Hypofibrinogenemia was demonstrated in 3 patients with leukemia in the present series, and all were thrombocytopenic.

Secondly, direct invasion of the brain and cerebral vessels by leukemic cells is not uncommon.[14,24,26,28,29] Such infiltrations adjacent to a cerebral hemorrhage have often been reported in the literature and were observed in 9 patients in the present series. Evidence has recently been presented to establish[28,29,32] and to deny[30] the significance of leukemic infiltrations in the pathogenesis of cerebral hemorrhage. A primary defect in the cerebral vessels has also been postulated.[30]

Leukemic infiltration of the meninges is also well recognized.[19,29,33,34,44] It has been specu-

TABLE 3
SITES OF INTRACRANIAL BLEEDING IN VARIOUS HEMATOLOGIC DISEASES

	Number of patients with					
	Hemorrhage within the brain					
Hematologic disease	*Multiple small hemorrhages*	*Solitary large* hemorrhages*	*Large* with multiple small hemorrhages*	*Subarachnoid hemorrhage*	*Subdural hemorrhage*	*Total*
Acute blastic leukemia	5	2	6	2	1	16
Myelogenous leukemia	4	1	4	0	2	11
Aplastic anemia	0	0	3	3	1	7
Myeloproliferative disease	2	1	0	1	0	4
Other thrombocytopenias	5	2	5	1	0	13
Hypoprothrombinemia	1	0	0	0	2	3
Hemophilia	0	2	0	2	0	4
Total	17	8	18	9	6	58

*Greater than 2 cm. in any diameter

lated[35] and refuted[28] that such infiltration may contribute to subdural or subarachnoid hemorrhage in leukemia. Leukemic infiltration of the brain and meninges may also produce signs and symptoms of increased intracranial pressure without intracranial bleeding.[20,22,29,35]

Leukemia was the most commonly encountered disease in the present series. Intracranial bleeding in patients with leukemia seemed to be more extensive than that in patients with other hematologic diseases, and the clinical courses seemed much more fulminating. Patients with leukemia also differed from other patients by showing retinal hemorrhages more frequently. It should be recalled that funduscopically observable bleeding may occur with leukemia without intracranial involvement. However, the presence of subhyaloid hemorrhages indicates intracranial hemorrhage.[21]

Lumbar puncture. There has been some discussion concerning the indications or contraindications of lumbar puncture in patients with bleeding tendencies.[36,37] The procedure has been considered dangerous because of the "fear of aggravating bleeding"[38] or inducing "bleeding in closed spaces" with resultant damage to the nervous system.[39] The possibility of cauda equina compression from such bleeding has led some physicians to consider a bleeding tendency an absolute contraindication for lumbar puncture. It is felt here, however, that the information to be gained from lumbar puncture in a patient with a bleeding tendency and suspected intracranial hemorrhage warrants the possible risk of the procedure. The evidence on which this belief is based will now be reviewed.

The signs produced by subarachnoid hemorrhage are quite similar to those of infection of the meninges, and differentiation of the two conditions by clinical means alone may at times be impossible. Such differentiation, of course, is definitely performed by lumbar puncture. Patients with blood dyscrasias are particularly susceptible to infection. Leukopenia, hypogammaglobulinemia, and corticosteroid therapy may all seriously impair their normal defense and immune mechanisms. In cases of bacterial meningitis, lumbar puncture may be the only means of obtaining the pathogen and subjecting it to appropriate sensitivity studies. Since the infections observed in patients with hematologic diseases are usually hospital-acquired ones, antibiotic therapy may be ineffective without such study. Another relatively frequent, now treatable, infectious agent of the central nervous system and meninges in patients with blood dyscrasias—Cryptococcus neoformans—may also be recognized and treated through lumbar puncture.

A third possible cause of a meningeal syndrome in leukemic patients—infiltration of the meninges—may be diagnosed by the detection of leukemic cells in the cerebrospinal fluid.[34,35]

Not only will lumbar puncture allow differentiation among bleeding, infection, and infiltration in the meninges, but it may also reveal information of value for the management of intracranial bleeding. Thus, bloody cerebrospinal fluid would indicate subarachnoid bleeding or intracerebral bleeding which has ruptured into the ventricles, while clear or xanthochromic fluid under increased pressure may suggest subdural or intracerebral bleeding. This differentiation is important prognostically as well as therapeutically. Lumbar puncture will also allow the intrathecal administration of chemotherapy[35,40,44] for leukemic infiltration and may at times be therapeutic by itself.[41]

Thus, there is considerable argument for the performance of lumbar punctures in patients with suspected intracranial bleeding. At the same time, there is scanty evidence that lumbar puncture is harmful in patients with bleeding tendencies.

Lumbar punctures were performed 49 times in 21 patients from the present series; at least an additional 130 punctures in patients with coagulation defects have been reported. The performance of 81 lumbar punctures in leukemic patients has recently been described.[29] Also, many patients with bleeding tendencies have undergone lumbar puncture at this hospital to exclude intracranial bleeding. In this collected group of over 200 spinal taps in patients with hemorrhagic tendencies, rare external bleeding at the puncture site has been the only noted complication.

It is felt, therefore, that a bleeding tendency does not in itself contraindicate lumbar puncture. However, since the theoretic possibility of internal bleeding exists, the procedure had

best be done by an experienced physician and an attempt should be made to correct the coagulation defect, if possible, before its performance.

Therapeutic considerations. The possibility of a coagulation defect should be considered in every patient with an intracranial hemorrhage; 4 patients in the present series were admitted to the hospital with signs and symptoms of intracranial bleeding before knowledge of their hemorrhagic diathesis. An adequate history and a careful general physical examination will usually allow recognition of a bleeding tendency, if one is present. Of the 58 patients with intracranial bleeding in the present series, 56 had evidence of bleeding elsewhere. Utilization of some of the laboratory procedures listed in Table 1 will, at times, also be necessary for full elucidation of the clotting defect.

The first and immediate goal in the treatment of an intracranial hemorrhage in a patient with a bleeding tendency is to restore hemostasis to as normal a state as possible. This can be done with varying success depending upon the nature of the coagulation defect and the disease producing it. Thus, hypoprothrombinemia can usually be treated with vitamin K and fresh whole blood; hypofibrinogenemia may be corrected by fibrinogen, and hemophiliac patients are usually responsive to fresh frozen plasma. The therapy for thrombocytopenia—regardless of cause—is usually less satisfactory. Such therapy consists of steroids, ACTH, fresh whole blood, and, if available, platelet transfusions. Chronic idiopathic thrombocytopenic purpura may respond to splenectomy. These measures must be initiated promptly with suspected intracranial bleeding. One of the patients with thrombocytopenia in the present series probably survived his intracranial hemorrhage because of an emergency splenectomy. Not only must therapy be instituted early, but frequent hematologic investigation is necessary to insure that therapy continues adequately. This is especially true of the replacement therapies, such as plasma and fibrinogen.

Once adequate hematologic control is achieved, consideration for special neurologic investigation and therapy may be undertaken. If the patient's neurologic status improves, he had best be left alone. If, however, the clinical picture shows continued downhill progression and there is a definite possibility of bleeding in an accessible site, percutaneous carotid arteriography may be considered, provided some hemostasis can be maintained. The indications for angiography in a patient with hemorrhagic diathesis, as well as the possible complication of bleeding from the puncture site and resultant tracheal compression, have been discussed elsewhere.[1]

The purpose of arteriography in the patient with intracranial hemorrhage and a bleeding tendency is to establish or exclude a sub- or epidural hematoma. Arteriography is preferable to trephination for the diagnosis of subdural hematoma in the patient with a coagulation defect because the site of possible bleeding from arteriography can at least be controlled by manual pressure. The exact location of the intracranial hemorrhage may also be determined. If arteriography demonstrates an intracerebral lesion, surgical intervention in the patient with a bleeding tendency is probably contraindicated; if extracerebral bleeding is demonstrated, arteriography may help the surgeon select the site for trephination. Strict attention must be paid to hemostasis during surgery, and the procedure should be undertaken only under hematologic supervision. It should be noted that patients with coagulation defects may bleed excessively during any form of surgery, even when preoperative laboratory tests have indicated some correction of the defects.

The preceding discussion is more than theoretic. Subdural hematomas do occur in patients with bleeding tendencies[2,32,35,42,43] and were found in 6 patients in the present series. Only 2 of the 7 patients who underwent neurosurgical intervention in the present series survived. A few reports of successful craniotomies or trephination in patients with blood dyscrasias have appeared in the literature; however, most of the survivals have been in patients with subdural bleeding.

The therapy for subarachnoid and intracerebral bleeding in patients with bleeding tendencies is at present supportive. It is possible that such therapies as hypothermia and induced hypotension may be applicable in the near future.

SUMMARY

Verified bleeding tendencies and proved intracranial hemorrhage were observed in 58 patients during a seven-year period. Intracranial hemorrhage tended to occur more often with those hematologic diseases producing thrombocytopenia. The bleeding was usually intracerebral, and multiple hemorrhages in the brain were frequently found at autopsy. Intracerebral hemorrhage was most severe in patients with acute leukemia.

A coagulation defect should be excluded in every patient with intracranial bleeding. Lumbar puncture can be performed, if indicated, in the presence of a bleeding tendency. Arteriographic investigation may at times be considered for the detection of a subdural hematoma.

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Ectopic pinealoma in the chiasma region

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PINEALOMAS are occasionally found at the time of surgical exploration or at autopsy to involve the infundibular region. Previous reports concerning pineal neoplasms include about 50 cases in which this region was involved. The authors of this communication have observed certain distinctions in the various manifestations of these tumors and wish to present additional cases as well as a classification based on differences in their location and clinical symptomatology.

Pinealomas involving the infundibular region can be classified into 3 types, according to the site of origin and mode of involvement. In each, certain distinguishing clinical features are evident.

The first type arises in the pineal region and metastasizes to the floor of the third ventricle with subsequent growth into the pituitary stalk, posterior lobe of the hypophysis, optic tract, and chiasm.

The second type is the ectopic pinealoma which arises in the third ventricle and invades the hypothalamus, pituitary stalk, neurohypophysis, and optic pathways.

The third type is the ectopic pinealoma in the chiasmal region located mainly outside of the brain. Again, as in the second type, the pineal body is intact. This neoplasm usually involves the floor of the third ventricle, the pituitary stalk, neurohypophysis, and optic pathways. Rarely, in very advanced cases, it may be difficult at autopsy to differentiate clearly between the second and third types of tumors.

Clinically, the symptomatology and course of the patient vary significantly in each group. In the first, symptoms associated with neoplasms in the pineal region as well as the hypothalamus occur. The tumors in the pineal region often produce symptoms of increased intracranial pressure, Parinaud's syndrome, Argyll Robertson symptom, double vision, hearing impairment, and, less frequently, pyramidal tract signs. Involvement of the hypothalamus causes additional symptomatology, such as diabetes insipidus, abnormalities in body temperature, and hypopituitarism.

In the second group, symptomatology is referable to destruction of the hypothalamus with increased intracranial pressure following growth of the tumor in the third ventricle. Occasionally, destruction of the thalamus also occurs.

In the third type, signs of increased intracranial pressure are very rare, except occasionally in the terminal stage of the disease. The tumor primarily involves the optic tract and chiasm, the pituitary stalk and gland, and the floor of third ventricle. Clinical manifestations commonly include primary optic atrophy, bitemporal hemianopsia, diabetes insipidus, and hypopituitarism.[40]

Recognition of the location of these neoplasms by their clinical manifestations has direct implications on the mode of therapy. In tumors of the first two groups, the location of the neoplasm is such that successful surgical resection is not feasible. In the third group, however, the clinical course can be lengthened and often vision can be preserved by surgical resection. Therefore, it is desirable to diagnose pinealomas of the third type preoperatively. Fourteen such cases have been reported in the literature, but no case was diagnosed correctly before operation or autopsy. As will be mentioned later, however, the symptoms of this

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type of tumor are quite characteristic, so that it may often be possible to establish a correct diagnosis preoperatively.

CASE REPORTS

Case 1. A 13-year-old female was admitted to the Pediatric Service of Kyoto University Hospital in May 1955 because of polyuria and polydipsia of six months' duration. No cause could be found for her symptoms. She was treated with posterior pituitary extract with a significant reduction in her daily output of urine, which previously had varied between 4 and 5 liters a day. Fifteen months later, she was admitted to the Neurosurgical Department because of headaches and visual disturbances of six weeks' duration. Examination revealed that visual acuity was 20/200 on the right, and finger counting was at 1 meter on the left. Visual field examination of the right eye revealed a temporal field defect. The visual field of the left eye could not be determined because of poor vision. Ophthalmoscopic examination revealed bilateral primary optic atrophy. The left pupil was larger than the right, and the latter reacted sluggishly to light. It was observed that her growth had stopped since the time of the first admission. There was no further significant physical finding. The daily urine output varied between 2 and 3 liters. Cerebrospinal fluid examination revealed a pressure of 160 mm. of water, normal protein, and no pleocytosis. Skull roentgenograms showed no abnormality. The sella turcica was normal in size, and no calcification was found in the intra- or suprasellar region.

On February 10, 1956, a left frontal craniotomy was performed. A firm, reddish tumor was found that compressed the left optic nerve from below. The left optic nerve was thickened; the right appeared normal. The tumor extended into the sella turcica; most of it was resected by curettage. Postoperatively, the patient's course was uneventful with some improvement in visual acuity of the right eye. There was no change in her daily urinary output.

Following hospitalization, visual acuity of the right eye had gradually improved, and, in September 1956, her right visual acuity was 20/25. From October 1956, the visual acuity of the right eye gradually decreased and diabetes insipidus also increased in severity, and she was again hospitalized on January 4, 1957.

At that time, the visual acuity of the right eye was 20/30, and the left eye was blind. Visual field examination revealed a nasal field and lower temporal quadrant defect of the right eye. Roentgen examination was normal except for slight thinning of the dorsum sellae. A right frontal craniotomy was performed, and no definite tumor mass was found between the optic nerves. There were some meningeal adhesions around these nerves, and the adhesions were detached. Postoperatively, she did well and vision in the right eye improved somewhat. Her final hospitalization was in August 1957 because of loss of vision in the right eye. There was no evidence of increased intracranial pressure. Cerebral angiography and pneumoencephalography failed to reveal any abnormality. She was given a course of roentgen therapy without evident improvement, and ultimately she became totally blind. For the following two years, her course remained essentially unchanged until October 1959, when she became bedridden. She had a gradual downhill course and died at home on November 29, 1959. No autopsy was performed.

Histologic examination of the specimen removed at surgery revealed a classical pinealoma (Fig. 1). The tumor consisted of 2 types of cells: large cells resembling epithelial elements and small cells similar in appearance to lymphocytes. The large cells were polygonal or spheroidal and contained abundant eosinophilic cytoplasm with large, round nuclei. These nuclei had coarsely granular chromatin and occasionally contained a prominent nucleolus. Mitotic figures were common and multinucleated giant cells were also present. The large cells failed to form any definite architectural pattern and were scattered in a connective tissue stroma closely intermingled with small lymphoid cells.

Case 2. This patient was a 16-year-old male who was admitted to the Neurosurgical Department of the Kyoto University Hospital on December 3, 1954. Eleven months prior to admission, he first noted slight blurring of vision which gradually became worse. For six months, he had noted polyuria and polydipsia. On examination, he was found to be normally developed. He was completely blind, and ophthalmoscopic examination revealed bilateral primary optic atrophy. No other physical abnormalities were noted. His daily urine output varied between 4 and 6 liters, with a specific gravity usually of 1.002. A lumbar puncture failed to reveal any abnormality; the fluid was normal and was under normal pressure. Roentgen examination of the skull was not revealing. On December 15, 1954, a

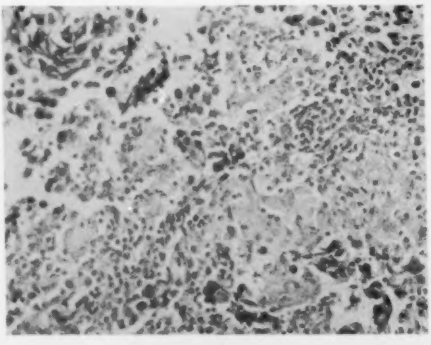

Fig. 1. *(Case 1).* Ectopic pinealoma in the chiasmal region. Note large and small cells of tumor. Hematoxylin-eosin stain. X 250

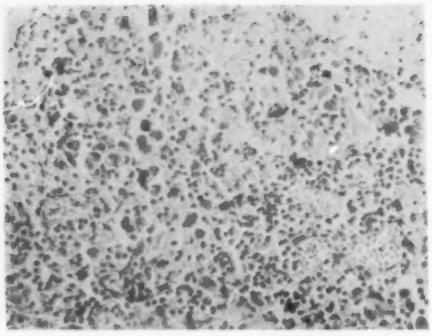

Fig. 2. *(Case 2).* Ectopic pinealoma in the chiasmal region. Hematoxylin-eosin stain. X 250

right frontal craniotomy was performed. A firm, pinkish tumor was found in the suprasellar region. The optic nerves and chiasm could not be seen. The tumor was biopsied, following which it bled considerably so that no further resection was attempted. Postoperatively, his course was uneventful and he was discharged from the hospital about two weeks after the operation. He died one month later at home; no autopsy was performed.

Histologic examination of the tumor biopsy revealed a pinealoma (Fig. 2). The tumor was composed of large epithelioid cells, small round cells, and an abundant connective tissue stroma. The large cells had no special architectural pattern, such as a mosaic arrangement, and were diffusely intermingled with small lymphoid cells and connective tissue. They were spherical or polygonal and contained eosinophilic cytoplasm with hyperchromatic round nuclei. Occasionally, nucleoli were prominent. The cytoplasm of some cells was vacuolated.

Case 3. This case was previously reported by Héon and Scoville.[11] The patient was a 12-year-old girl. When she was 9 years of age, she was admitted to the Hartford Hospital in Hartford, Connecticut, with a one-year history of polydipsia and polyuria. Her daily output of urine was 2 to 4 liters, and the specific gravity was 1.008.

Her vision and visual fields were normal until September 1948, when they began to fail. The child's physical development during the three-year interval between admissions was definitely retarded. She was admitted to the Hartford Hospital on December 31, 1948. Physical examination revealed a small child who was slightly obese. Ophthalmoscopic examination revealed bilateral primary optic atrophy. Visual field examination showed an advanced defect of the chiasmal type with only residual nasal vision remaining on the left.

X-ray films of the skull failed to reveal any definite abnormalities, although the anterior clinoid processes were thought to be slightly depressed. Pneumoencephalography showed that the ventricular system was normal except for elevation of the anterior portion of the floor of the third ventricle. The basal cisterns were well filled except that the cisterna chiasmatis was not visualized.

On January 4, 1949, a right frontal craniotomy was performed. A grayish tumor was found around the optic chiasm, which appeared to invade the right optic nerve. No definite capsule about the tumor was noted, and it appeared to involve the floor of the third ventricle. The tumor tissue around the optic chiasm was partially removed. After the operation, the patient remained in coma for thirty-six hours and then died.

General autopsy showed nothing save that body and organ weights were slightly and consistently below the normal values for a 12-year-old child.

The sella turcica was normal in size, and the pituitary body appeared normal. The cerebrum was quite edematous, and the floor of the third ventricle, the chiasm, pituitary stalk, and the pituitary fossa were enveloped by a soft, blood-stained gray mass. This mass extended posteriorly along the floor of the third ventricle up to the cerebral peduncles. The ventricular system was not dilated.

Sections of the tumor were reviewed at Montefiore Hospital through the kindness of Dr. Ronald Beckett. The tumor was composed in part of large, polyhedral cells with abundant cytoplasm and somewhat pleomorphic, often vesicular nuclei. These were present in small masses or were dispersed in a fibrous stroma containing numerous small round cells which resembled lymphocytes. Tumor extensively replaced the posterior lobe of the hypophysis and invaded the floor of the third ventricle. The anterior lobe of the hypophysis was, for the most part, intact, and the pineal body was histologically normal.

DISCUSSION

Previous reports include 14 cases of pinealomas which correspond to those of the third type. In addition, several other cases have been reported under other diagnoses, such as encephalitis, optic glioma, sarcoma, and carcinoma, which would seem to be pinealomas according to the microscopic descriptions. The clinical course and symptomatology of these tumors are quite similar and unique and are summarized in the table. Characteristically, diabetes insipidus, visual disturbances (primary optic atrophy and bitemporal hemianopsia) and hypopituitarism are the 3 most common and consistent symptoms distinguishing this group. The onset of symptoms appears most frequently at the end of the first or during the second decade of life. In almost all cases, the onset was under the age of 25

CASES OF TYPE 3 PINEALOMA

Author	*Case*	*Initial symptom*	*Diabetes insipidus*	*Visual disturbance*	*Hypopituitarism*	*Other symptoms*	*Dilation of sella turcica*
Starck[28]	Male 25 yrs.	Diabetes insipidus	+	+	Adiposogenital dystrophia	–	–
Gautier, Jentzer, and de Morsier[14]	Female 14 yrs.	Diabetes insipidus	+	+	–	–	–
Akamatsu[1]	Male 22 yrs.	Diabetes insipidus	+	+	Hypogonadism, retarded growth	Headache	–
Russell and Sachs,[32] Case 5	Female 10 yrs.	Visual disturbance	+	+	–	Headache, nausea, vomiting	Slightly enlarged
Russell,[31] Case 3	Male 14 yrs.	Diabetes insipidus	+	+	Hypogonadism, retarded growth	Headache	–
Russell,[32] Case 4	Female 10 yrs.	–	+	+	–	–	–
Horrax and Wyatt,[20] Case 2	Male 12 yrs.	Visual disturbance	+	+	Retarded growth	Headache, nausea, vomiting	Slightly enlarged
Troland and Brown[41]	Male 14 yrs.	Precocious puberty	– (after operation +)	–	–	Headache, nausea, precocious puberty	–
Rand and Lemmen,[30] Case 3	Female 15 yrs.	Diabetes insipidus	+	+	Retarded growth, hypogonadism	–	–
Kahn[23]	Female 13 yrs.	Diabetes insipidus	+	+	Panhypopituitarism	Somnolence, abnormality in temperature	–
Sasano et al.[34]	Male 20 yrs.	Diabetes insipidus	+	–	Hypogonadism	–	–
Løken,[25] Case 2	Male 41 yrs.	Diabetes insipidus	+		–	–	–
Busch,[9] Case 2	Male 32 yrs.	Diabetes insipidus	+	+	Hypogonadism	Right pyramidal sign	–
Héon and Scoville,[17] Case 1	Male 12 yrs.	Diabetes insipidus	+	+	Retarded growth	Headache	–
Kageyama and Belsky, Case 1	Female 13 yrs.	Diabetes insipidus	+	+	Retarded growth	–	–
Kageyama and Belsky, Case 2	Male 16 yrs.	Visual disturbance	+	+	–	–	–

years. There appears to be no sex predominance. Most frequently, diabetes insipidus is the initial symptom. It may be the only symptom for many months or even years. Occasionally, either visual disturbances or hypopituitarism may be the first symptoms. Of the 3 major symptoms, diabetes insipidus is most characteristic and appeared in almost all cases. The degree of severity varied between 3 and 6 liters.

Visual disturbances are also noted in almost all cases. They are due to compression or infiltration of the optic tracts, nerves, or chiasm by neoplasm. Compression by the tumor was found in many cases, and visual acuity recovered after resection of the tumor. However, infiltration of the tumor into the optic tract or chiasm was also noted macroscopically as well as microscopically in many cases. Macroscopically, these infiltrations were characterized by gross thickening of the optic tract or nerve. Clinically, visual field examination usually showed bitemporal hemianopsic defects and ophthalmoscopic examination revealed bilateral primary optic atrophy. Papilledema or choked disk was rarely seen.

Hypopituitarism has been observed in most cases. In cases in which the tumor arose before puberty, dwarfism occurred, and, after puberty, hypogonadism was predominant. Usually, no dilation of the sella turcica was seen on roentgen examination, although, in some cases, thinning of the posterior clinoid processes was seen. The hypopituitarism in the absence of changes in the sella turcica seemed to be due to the infiltrative nature of the tumor and to destruction of the hypothalamus. In Sasano's[34] case and in our case 3, the anterior lobe of the pituitary gland was histologically normal, although both of these cases had definite signs of hypopituitarism. It would seem that in these instances, destruction of the hypothalamus was of major significance in this regard. Until the terminal stage, almost all cases showed no signs of increased intracranial pressure.

Because of the diffuse infiltrative growth and lack of large mass lesions, plain skull roentgenograms and cerebral angiography are often not very helpful in establishing the diagnosis. As the neoplasm frequently develops behind the optic chiasm, pneumoencephalography may be of diagnostic value and may show an elevation and irregularity of the floor of the third ventricle and an air-filling defect in the cisterna chiasmatis.

DIFFERENTIAL DIAGNOSIS

Pituitary adenoma. Symptoms of visual disturbance, particularly with reference to the optic chiasm (bitemporal hemianopsia and primary optic atrophy), hypopituitarism, and the absence of signs of increased intracranial pressure, are common to both pituitary adenomas and ectopic pinealomas in the chiasmal region.[44] Pituitary adenomas occur usually in adults over the age of 25, whereas ectopic pinealomas of this type are most often seen in the age group under 25.[3,4,16,19] X-ray findings offer certain additional distinctions. Destruction of the sella turcica is a common finding in pituitary adenomas and is not seen in pinealomas. Also, cerebral angiography may reveal elevation of the A_1 portion of the anterior cerebral artery in cases of pituitary adenomas. This finding is not seen in ectopic pinealomas. The presence or absence of diabetes insipidus is most helpful in differentiating these tumors. This symptom was present in almost all cases of ectopic pinealomas in this region and was also the initial sign of the disease in about two-thirds of them.[39] Cases of pituitary adenomas, however, are very rarely associated with diabetes insipidus.

Craniopharyngioma. About 20 to 30% of craniopharyngiomas are associated with diabetes insipidus, while, with ectopic pinealomas, this incidence approaches almost 100%. In the former, this rarely appears as the initial symptom. In craniopharyngiomas, the type of visual disturbance varies greatly from case to case.[26] There may be papilledema, secondary optic atrophy as well as primary atrophy, homonymous hemianopsia, and concentric field narrowing as well as bitemporal hemianopsia. Increased intracranial pressure may commonly occur in cases of craniopharyngioma as a result of its large mass. As noted before, however, this finding is rarely seen in ectopic pinealomas in the chiasmal region until the terminal stage. Most cases of craniopharyngioma are associated with dilation or destruction of the sella turcica, and virtually one half show calcification in the intrasellar or suprasel-

lar region on roentgen examination. With cerebral angiography, an elevation of the A_1 portion of the anterior cerebral artery is frequently found in craniopharyngiomas but is not seen in ectopic pinealomas. Pneumoventriculography in craniopharyngiomas often shows dilation of the lateral ventricles, obstruction of the foramen of Monro, or a filling defect of smooth surface in the anterior portion of the third ventricle. Pneumoventriculography in pinealomas may also show this filling defect in the third ventricle, but it is usually less marked. When it is seen in pinealomas, the edge of the defect appears irregular, whereas it is usually smooth in craniopharyngiomas.

Meningioma. In general, meningiomas arising from the region of tuberculum sellae are seen in a much older group of patients. They may often be associated with bitemporal hemianopsia and primary optic atrophy without any signs of increased intracranial pressure. The sella turcica is also usually intact. Cases of this kind with diabetes insipidus have not been found in the literature. Moreover, this type of tumor is rarely associated with hypopituitarism. Cerebral angiography is helpful in further differentiating this neoplasm.

Infundibuloma. This glioma is also an infiltrative tumor and involves the pituitary stalk and floor of the third ventricle. The symptoms, however, would appear to be quite different. Until now, 9 cases of infundibuloma[43] have been reported, and none of these was associated with diabetes insipidus or bitemporal hemianopsia. These cases most commonly had signs of increased intracranial pressure and oculomotor palsies.

Astrocytoma. This tumor usually occurs in children in the anterior portion of the floor of the third ventricle. Usually, the tumor grows in the third ventricle, followed by obstruction to the pathway of the ventricular fluid. Therefore, in most cases, the predominant symptom is increased intracranial pressure. Sometimes, these tumors are associated with signs of precocious puberty. However, diabetes insipidus is very rarely found in these cases. Hypopituitarism or visual disturbances of the chiasmal type are rarely seen.

Sarcoidosis. The symptoms of sarcoidosis involving the central nervous system vary greatly from case to case depending on the location of lesions. However, diabetes insipidus and visual disturbances are fairly frequent findings. Pennell[29] found 18 cases associated with diabetes insipidus in a series of 51 cases of sarcoidosis involving the central nervous system. However, the character of the visual disturbances is quite different and is usually due to uveitis or retinitis.

Metastatic neoplasms. Occasionally, metastatic tumors occur in the infundibular region and may be associated with diabetes insipidus. Such tumors as carcinoma of the breast, stomach, and lung; malignant melanoma; and lymphosarcoma have been reported. Differentiation from the ectopic pinealoma of the chiasmal region can be established usually on the basis of age, destruction of bone (particularly the sella turcica), and the clinical history with reference to extracranial signs.

RELATIONSHIP BETWEEN TERATOMAS AND ECTOPIC PINEALOMAS IN THE INFUNDIBULAR REGION

Dorothy Russell[31] observed that many of the so-called pinealomas are teratoid tumors and, particularly, that ectopic pinealomas are teratomatous in nature. She reported 3 ectopic pinealomas in which teratomatous components, such as columnar epithelium, epidermoid foci, cartilage, and muscle, were found. In undisputable typical teratomas of the pineal body, foci of pinealomatous structures also occur. In 1947, Friedman[12] demonstrated a morphologic similarity between pinealomas of the 2-cell type pattern and seminomas and referred to these pinealomas as germinomas. In this regard, distinctions between intracranial teratomas and pinealomas, particularly ectopic pinealomas, are often not clear on morphologic grounds. Furthermore, the clinical manifestations of these types of tumors are often similar, as their sites of origin and manner of growth are often similar.

Ectopic pinealomas and teratomas have many characteristics in common when they involve the infundibular region. Intracranial teratomas arise most frequently in the pineal region; however, they may arise anywhere along the midline from the pineal body to the hypophysis. They have been described in the third ventricle,[35,2,21,27,36] in the suprasellar region,[24,15,11,7,27,37] and in the intrasellar re-

gion.[5,8,28] In these cases, or in those cases of teratomas involving the pineal region, a pinealomatous component was frequently found in the teratoma with extension or metastasis of this component involving the infundibular region, including the pituitary stalk, neurohypophysis, and, occasionally, the optic pathways.[6,2,10,42,37,32,22,15] These sites are similar to those which ectopic pinealomas involve and, as such, the clinical manifestations are usually identical. The following case is an example of such a teratoma in which pinealomatous elements were found involving the pituitary stalk and tuber cinereum.

Case 4. This case was reported by Fukushima[13] among several patients with precocious puberty. This patient was a 9-year-old male who was admitted to the Neurosurgical Department of Kyoto University Hospital in March 1956. Fourteen months before, diabetes insipidus had developed with a daily urinary output that at times reached 15 liters. Seven months after the onset of diabetes insipidus, growth of pubic hair was first noted. One month prior to hospitalization, headaches, vomiting, ptosis of the right eyelid, and diplopia developed. Physical findings revealed a right oculomotor paralysis and a slightly dilated sella on x-ray films. He was markedly weak and emaciated. He gradually deteriorated and died two weeks after admission to the hospital.

Endocrine function studies revealed that twenty-four-hour total urinary gonadotropins, using kaolin absorption, varied between 24 and 48 mouse uterine units. The urinary 17-ketosteroids were 0.25 mg. in twenty-four hours. The urinary excretion of corticoids following administration of ACTH was decreased. The basal metabolic rate was minus 56.

Autopsy revealed evidence of precocious puberty with enlargement of the penis, testicles, and prostate. In the region of the pituitary body, there was a tumor measuring 8 cm. in diameter, which was firm and dark red in color. The entire pituitary was completely replaced by tumor and the right oculomotor, trigeminal, and abducens nerves were embedded in the mass. The pituitary stalk was thickened to 4 times its normal size. Coronal sections of the brain revealed no dilation of the ventricles. Grossly, the pineal body appeared normal. The thymus was atrophied and the thyroid and adrenals also were small and atrophic in appearance. Multiple small focal hemorrhagic lesions were noted in both lungs. There was generalized lymph node enlargement.

Microscopically, the tumor mass in the hypophysis was partially necrotic and hemorrhagic. In preserved zones, 2 types of tissue were identified. The first had a teratomatous nature and included squamous epithelium, mucous glands, liver parenchyma, cartilage, and angiomatous tissue (Fig. 3). The second component was histologically identical with a choriocarcinoma (Fig. 4). Cytotrophoblast cells predominated, but cells resembling syncytial trophoblasts were also present. Sections of the pituitary stalk revealed a third type of tissue (Fig. 5) which infiltrated and replaced this structure and consisted of large, irregularly shaped cells with clear nuclei interspersed with small cells resembling lymphocytes. This tissue had the appearance of a pinealoma. The lungs contained numerous metastatic foci of tumor which had the appearance of choriocarcinoma (Fig. 6). The adrenal cortex was atrophic with the zona fasciculata being most affected. The thyroid follicles were large and lined by flattened epithelium. The prostatic glands were well developed and numerous. Careful examination of both testes failed to reveal any neoplasm. Spermatogenesis was more advanced than is normal for a 9-year-old boy, and there was slight increase in the number of interstitial cells. Sections of the brain revealed infiltration of the pinealomatous component of the tumor into the tuber cinereum extending to the subependymal region of the third ventricle. The dorsomedial nuclei of the hypothalamus were destroyed, and there was cell loss and degeneration of the posterior and paraventricular nuclei. The nuclei in the preoptic, lateral, and dorsal hypothalamic area and mammillary bodies were intact. The pineal body was grossly normal, but, microscopically, some large cells simulating tumor cells in the pituitary stalk were found in parts. However, the wall of the third ventricle was intact.

COMMENT

Case 4 illustrates the relationship between ectopic pinealomas and teratomas. The infiltration of pinealomatous tissue in the pituitary stalk and the floor of the third ventricle closely resembles the behavior of ectopic pinealomas in the infundibular region.

This teratoma had 2 malignant components, choriocarcinomatous and pinealomatous tissue. Extracranially, it is not uncommon for a choriocarcinoma to be accompanied by a germinoma in a teratoma. These combinations have been seen in the testicular, mediastinal, or retroperitoneal teratomas. Moreover, Friedman[12] indicated that so-called pinealomas are identical with germinomas. Therefore, it is considered more reasonable that the pinealomatous tissue in this case should be considered as a germinoma.

Considering the close similarity between ectopic pinealomas and teratomas in the infundibular region, it might be more reasonable to consider all these ectopic pinealomas as germinomas.

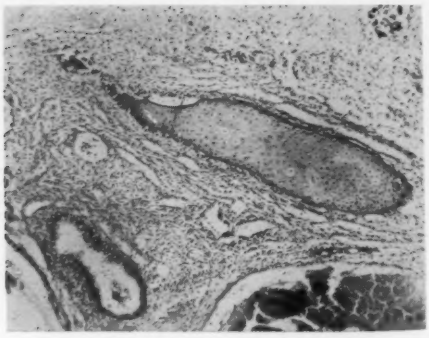

Fig. 3. *(Case 4).* Cartilage and mucus-secreting epithelium in the pituitary teratoma. Hematoxylin-eosin stain. X 100

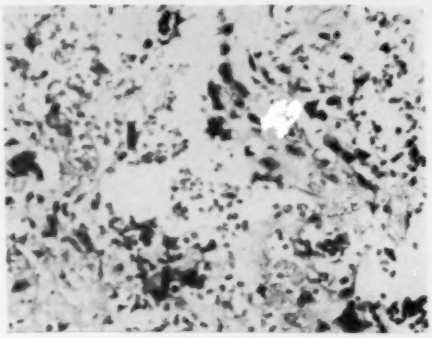

Fig. 4. *(Case 4).* Choriocarcinomatous tissue in the pituitary teratoma. Hematoxylin-eosin stain. X 300

TREATMENT

Usually, in cases of pinealomas of the first or second type in the infundibular region, resection or removal of the primary neoplasm, even if it is partial, causes a high operative mortality, and complete removal is not feasible. The follow-up studies of patients with pineal tumors[18,30] indicated that the results of a decompression procedure, such as Torkildsen's operation, followed by roentgen treatment were better than those obtained with radical operations. Therefore, for first or second type pinealomas, a decompression operation with irradiation to the third ventricle or pineal region as well as the infundibular region is considered the treatment of choice.

In the third type, however, removal of the neoplastic tissue is recommended in order to preserve visual acuity. As mentioned before, visual disturbances are due to compression or infiltration by the tumor. Some patients regained visual acuity after the removal of the compressing mass. Moreover, this tumor grows rather slowly, so that good visual acuity may be expected to be maintained for several months or years after the operation. In Horrax and Wyatt's[20] case 2 and Troland and Brown's[41] case, the patients maintained

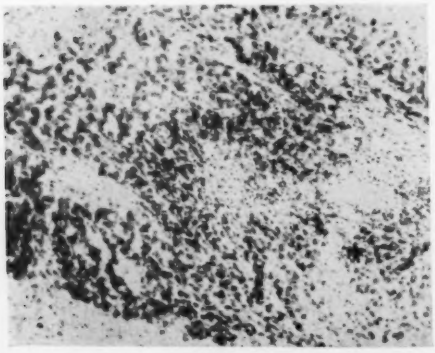

Fig. 5. *(Case 4).* Pinealomatous tissue in tuber cinereum. Hematoxylin-eosin stain. X 150

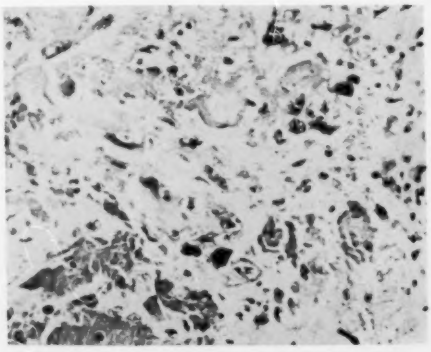

Fig. 6. *(Case 4).* Choriocarcinoma in lung (metastases). Hematoxylin-eosin stain. X 275

normal visual acuity for more than four and two years, respectively. In our case 1, visual acuity was regained and maintained for about one and a half years. Therefore, resection of the tumor and decompression of the optic nerves or chiasm would seem worthwhile.

At the time of operation, it must be kept in mind that these tumors infiltrate the floor of the third ventricle, so that no attempt should be made to remove the upper part of the tumor near the hypothalamus. Only the tumor tissue around the optic nerves and chiasm and in the sellar region should be removed.

Postoperative roentgen treatment to the remaining tumor tissue may be of value, since many consider these tumors to be radiosensitive. Both Horrax and Wyatt's[20] case 2 and Troland and Brown's[41] case underwent roentgen treatment following operation with favorable results.

SUMMARY

1. A classification of 3 types of ectopic pinealomas involving the infundibular region is presented based on the site of origin of the neoplasm and differences in the clinical manifestations of each type.

2. Ectopic pinealomas which involve the infundibular region are usually associated with a characteristic triad of clinical symptoms consisting of diabetes insipidus, visual disturbances, and hypopituitarism.

3. Diabetes insipidus occurs in almost all cases and is often the initial symptom. Visual disturbances are usually present and include visual field defects of the chiasmal type and optic atrophy. Hypopituitarism is a frequent finding and is associated with dwarfism in tumors arising before puberty and hypogonadism in those occurring after puberty.

4. Pinealomas arising primarily in the infundibular region can be differentiated from those which arise elsewhere and involve the infundibular region by direct extension or metastasis on the basis of absence of symptoms referable to obstruction of the third ventricle or symptoms associated with neoplasms in the region of the quadrigeminal plate.

5. Ectopic pinealomas and intracranial teratomas have certain morphologic similarities. The clinical manifestations of these tumors are also quite similar, depending on the sites of involvement.

6. In the therapy of pinealomas in the chiasmal region, surgical resection of a portion of the tumor is feasible and advantageous in preserving vision and prolonging life. Radiation therapy in conjunction with surgical resection may have a further palliative benefit.

We are indebted to Dr. Chisato Araki, professor of First Surgical Division of Kyoto University in Japan, for permission to use cases of his department in this paper. Also, acknowledgment is made to him and Dr. H. M. Zimmerman, chief, Laboratory Division, Montefiore Hospital, for their help and advice.

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Cortical cerebellar degeneration with ovarian carcinoma

W. Ian McDonald, B.Med.Sc., M.B.

SPECIFIC NEUROLOGIC COMPLICATIONS of carcinoma independent of metastasis are uncommon. Although their occurrence has been recognized for many years, they have been described in detail only in the past decade. More recently, nervous system damage unassociated with significant infiltration or local pressure has been recorded with myeloma,[1] the reticuloses,[2–5] and lymphatic leukemia.[3] The carcinomatous neuromyopathies have been classified by Brain and Henson[6] into 4 main groups: [1] cortical cerebellar degeneration, [2] peripheral neuropathy, [3] a "mixed" or encephalomyelitic form, and [4] neuromuscular disorders. These categories are not always clear-cut, but cortical cerebellar degeneration and sensory neuropathy are seen in pure form more frequently than the others. The following case of carcinomatous cortical cerebellar degeneration was diagnosed some four weeks before an underlying carcinoma was revealed by a secondary lymphatic deposit.

CASE REPORT

Miss I.F., aged 62, was admitted to the Christchurch Hospital on June 29, 1957, because of increasing difficulty in writing and unsteadiness in the legs.

She had been in excellent health until two years previously, when she had burnt her buttocks. This necessitated skin grafting. Since then, she had been vaguely unwell. A year before admission, she had symptoms of a peptic ulcer, which settled after several months of conservative treatment. Two months before admission, she had an influenza-like illness accompanied by persistent nausea. She had no jaundice, but liver function tests at this time showed abnormal flocculation tests (see table). About a month before admission, while recovering from this episode, she found that writing was becoming difficult and, a fortnight later, that she was losing control of her right leg. Soon after this, she began to notice clumsiness of the left arm and leg. By the time she was admitted, two weeks later, walking had become difficult and writing impossible. Apparently, a sister had had ataxia and died after a "stroke" in a mental hospital. Unfortunately, no further details were available.

On admission, the patient was seen to be a thin, intelligent woman. She had lost about 7 lb. in weight in the previous month. She was right-handed.

Physical examination revealed a right Horner's syndrome said to have been present since childhood. She had no nystagmus, and other cranial nerves were normal. Incoordination in all 4 limbs was noted, more marked on the right than on the left. Tendon jerks were brisk and symmetric. The right plantar reflex was flexor and the left equivocal. Nutrition, tone, power, and sensation were normal. Examination of other systems revealed only a small nodular goiter and bilateral pes cavus. Blood pressure was 165/95. A diagnosis was made of cortical cerebellar degeneration, probably secondary to a carcinoma of undetermined site.

A week after admission, vertigo, nausea, diplopia, and a feeling of falling backward became troublesome. Nystagmus on lateral gaze appeared and, a week later, vertical nystagmus as well. About three weeks after admission, she became depressed. During this time, incoordination on the left side became much worse but was still less than on the right side. Dysarthria also developed. The plantar reflexes were now definitely flexor and the tendon jerks a little brisker on the right than on the left.

From the Department of Physiology, University of Otago Medical School, Dunedin, New Zealand.

RESULTS OF LIVER FUNCTION STUDIES

Test (normal values in brackets)	*Date*			
	May 7 1957	July 1 1957	July 23 1957	August 13 1957
Thymol turbidity (0 to 4 units)	15	15	15	10
Thymol flocculation (normal, no flocculation; complete reaction, 4+)	4+	4+	3+	3+
Zinc sulfate turbidity (2 to 8 units)	20	20	20	20
Serum alkaline phosphatase (4 to 15 King-Armstrong units)	8	11	8	7
Serum bilirubin (0.2 to 1 mg.%)	0.4	1.0	0.6	0.8
Serum protein, total (6.0 to 8.0 g. %)		9.8	9.0	7.8
Serum albumin (3.8 to 5.5 g. %)		5.1	5.1	3.9
Serum globulin (1.8 to 3.0 g. %)		4.7	3.9	3.9
Albumin: globulin ratio (3:2)		1:1.1	1:1.3	1:1

A left supraclavicular lymph node was felt about a month after admission. Biopsy of this showed adenocarcinoma of undetermined origin. A chest roentgenogram was normal, and still no masses could be felt either abdominally or vaginally.

In these early stages of the illness, fluctuation in severity of the cerebellar signs was a marked feature, but, as time went on, the patient became progressively more ataxic and dysarthric and had titubation and static tremor in the arms. The goiter increased in size as the illness progressed. Two months after admission, she was completely bedridden. Her depression increased and was at times profound. She suffered no obvious intellectual deterioration. The distressing symptoms associated with ataxia and titubation were somewhat alleviated temporarily after administration of ethopropazine hydrochloride.

Some three months after admission, a mass became palpable in the right iliac fossa. It increased rapidly in size and finally pointed to the right labium majus, where it discharged staphylococcal pus. The patient's condition deteriorated steadily after this, and she died seventeen and a half weeks after admission.

Laboratory investigations. On admission, *blood findings* were packed cell volume, 44; white blood cell count, 5,000 per cubic millimeter with a normal differential count; and erythrocyte sedimentation rate (Wintrobe), 28 mm. in one hour. The sedimentation rate rose steadily to 52 mm. in one hour six weeks before death. On July 1, three days after admission, *cerebrospinal fluid findings* were white blood cell count, 6 per cubic millimeter; red cell count, 30 per cubic millimeter; and total protein, 30 mg. per cent, with slight increase in globulin (Pandy). On July 23, three weeks after admission, white cell count was 25 per cubic millimeter with 100% lymphocytes; red cell count, 8 per cubic millimeter; total protein, 30 mg. per cent with slight increase in globulin; and Maclagan's colloidal gold, 122221. On August 1, five weeks after admission, white cell count was 27 per cubic millimeter with 2 polymorphs and 25 lymphocytes; red cell count, 4 per cubic millimeter; total protein, 40 mg. per cent with moderate increase in globulin; and Maclagan's colloidal gold, 443210.

Liver function tests were persistently abnormal, showing strongly positive thymol flocculation tests and raised zinc sulfate and thymol turbidity tests but normal serum bilirubin. Latterly, there was a relative rise in the total globulin (see table).

Examinations of urine, of feces for occult blood, and of sputum for malignant cells were negative.

Roentgenograms of chest and skull and a lumbar encephalogram were normal. The lower cervical spine showed well marked degenerative changes.

Autopsy. Positive findings at postmortem

Fig. 1. Cerebellar cortex showing complete absence of Purkinje cells. Hematoxylin and eosin. × 120

examination seven hours after death were as follows.

Gross. The body was that of an emaciated, middle-aged woman. A septic wound was noted in the right inguinal region. Scattered old adhesions were seen in the pleural cavities. In the lungs, there was basal congestion with some areas of hemorrhagic consolidation. A small amount of fibrinous exudate was noted in the pericardial cavity. The heart was of normal size, but the myocardium was friable. The mitral valve showed roughening of the posterior cusp, with vegetations mainly on its posterior aspect and involving the chordae. From these, there was a heavy growth of staphylococcus aureus. Slight atheroma of the coronary arteries and aorta was found. Neither atheroma nor aneurysm was noted in the cerebral arteries.

The liver was firm and brownish; the gallbladder contained a solitary calculus. The spleen was of normal size and showed a small infarct. Slight nephrosclerosis and small embolic abscesses in both kidneys were noted. The thyroid showed a colloid nodular goiter.

The left ovary was replaced by a tumor some 5 cm. in diameter, adherent to the pelvic wall and fallopian tube. The right ovary, about 2 cm. in diameter, was also invaded by tumor. Lymph nodes containing tumor were found in the pelvis, along the abdominal aorta, and in relation to the pancreas. Plaques of tumor tissue were found in the pouch of Rutherford Morrison and on the pelvic peritoneum.

The brain looked normal. No gross evidence of secondary deposits or atrophy was found.

Microscopic: Ovary. A poorly differentiated adenocarcinoma, with solid alveoli in which there was some acinar formation, was found.

Liver. Changes of chronic venous congestion only were present, with no evidence of recent infectious hepatitis.

Central nervous system. The cerebellum showed diffuse loss of Purkinje cells. In many low-power fields, not a single Purkinje cell was visible (Fig. 1), although in some areas there were a few normal or shrunken cells (Fig. 2). Axon preparations (Holmes' silver method) showed that the baskets were preserved. Glial reaction was not marked; in some areas there was none, but here and there astrocyte proliferation was seen where the Purkinje cells were lost. The granular and molecular layers were normal. Myelin stain (Loyez) revealed no abnormality. A microscopic secondary deposit and a recent miliary abscess was seen in the cerebellar cortex.

Sections from the cerebral cortex, pons, medulla, and spinal cord showed neither significant abnormalities of the ganglion cells nor myelin degeneration. A microscopic miliary abscess was noted in the hippocampal cortex.

The leptomeninges from both the brain and spinal cord showed infiltration with mononuclear cells (Fig. 3). Similar cells were seen cuffing small blood vessels in the meninges and in the spinal cord, brain stem, cerebellum, and cerebral cortex (Fig. 4).

Fig. 2. Cerebellar cortex showing a few surviving Purkinje cells. Hematoxylin and eosin. × 120

In summary, the findings were [1] metastasizing adenocarcinoma of the ovary, [2] subacute cortical cerebellar degeneration, and [3] terminal staphylococcal septicemia.

COMMENT

This case of metastasizing carcinoma of the ovary with a subacute course of ataxia, vertigo, dysarthria, diplopia, nystagmus, cerebellar deficit in the limbs, and mental change progressing in two months to complete disablement is typical of carcinomatous cortical cerebellar degeneration. Typical too are the lymphocytic pleocytosis, raised globulin, and paretic colloidal gold curve in the cerebrospinal fluid. The selective loss of Purkinje cells in the cerebellum (Fig. 1) is characteristic, and mononuclear infiltration of the meninges (Fig. 3) and cuffing of central nervous system vessels (Fig. 4) are also seen.

Flocculation tests are a useful guide to the serum protein pattern.[7] The zinc sulfate turbidity test in particular is a good index of the gamma globulin. In the present case, flocculation tests were persistently abnormal from the time of the influenza-like illness, two months before admission, until the last determination, two months before death. Although this may have represented an attack of subicteric hepatitis, the absence of any postmortem sign of recent liver disease—other than venous congestion—is against this. On the other hand, the raised gamma globulin as revealed by the zinc sulfate turbidity test may have been related to some underlying allergic process. The patient was not obviously myxedematous, but it is interesting to note the presence of a nodular goiter which increased in size during the illness. The family history was indefinite. Perivascular cuffing and abnormal cerebrospinal fluid findings are not found in the hereditary ataxias.

DISCUSSION

Carcinomatous cortical cerebellar degeneration is characterized clinically by its subacute course, bilateral cerebellar signs, and the frequent association of dementia. It is usually progressive, developing in a few weeks or months, but may become arrested.[6,8] Most patients die within a few months to two and one-half years. Rarely, the cerebellar symptoms may disappear and the cerebrospinal fluid revert to normal after successful removal of the tumor.[9] The symptoms may appear before the tumor is clinically evident (as in the present case), after its discovery, or even up to seven months after its successful removal.[8] Nystagmus, diplopia, dysarthria, vertigo, nausea, ataxia, and cerebellar deficit in the arms and legs are usual, and static tremor, spontaneous movements, and shooting pains in the legs may occur. The plantar reflexes may be extensor, and the tendon jerks are variable. Dementia is common, but depression with or without agitation may be seen.

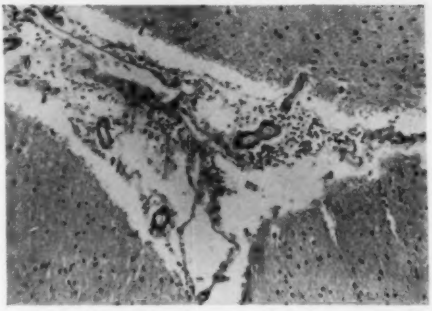

Fig. 3. Leptomeninges from the cerebellum showing infiltration with mononuclear cells. Hematoxylin and eosin. × 120

Pathology. Neuronal degeneration principally affects the Purkinje cells, which are usually involved throughout the cerebellum; occasionally, however, degeneration may be

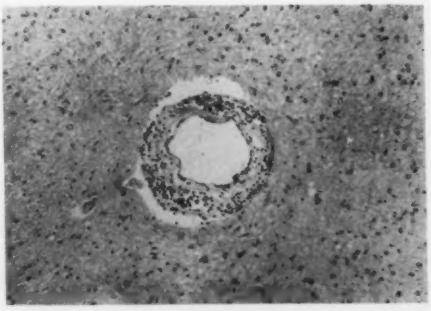

Fig. 4. Medulla showing cuffing of a small blood vessel with mononuclear cells. Hematoxylin and eosin. × 120

patchy, with some areas where more or less damaged cells are preserved. This selective Purkinje cell degeneration is seen especially with carcinoma of the bronchus, breast, and ovary[10,11] but may occur with uterine carcinoma.[12,13] The same appearances were present in Brouwer's case[14] of "polymorphic cell sarcoma" of the pelvis; no histologic details of the primary tumor were given, however, and it seems possible that the tumor may have been an anaplastic carcinoma. Usually, some glial reaction occurs in the molecular layer, involving either or both the astrocytes and microglia.[10,11]

Degeneration of nerve cells and fibers elsewhere in the central nervous system may accompany Purkinje cell degeneration in some cases. Early degeneration may be found in the dorsal roots, superior cerebellar peduncles, and spinocerebellar and other long tracts of the spinal cord.[10,15] The dentate and other central cerebellar nuclei may show degenerative changes,[15] but the olives and nuclei pontis are very rarely affected.[16] Degeneration of the corpus luysii and of strioluysial fibers may occur.[15] Despite the frequent occurrence of dementia, representative sections of the cerebral cortex usually show no significant changes.[6] In more acute cases, infiltration of the meninges and lymphocytic cuffing of cerebellar, brain stem, and spinal cord vessels may be seen.[6,10,15,16] The cerebellum contains insignificant secondary deposits or none at all.

The primary tumor itself is usually an adenocarcinoma in one of the sites already mentioned. In addition, a transient cerebellar syndrome has been described with carcinoma of the colon.[9]

Degeneration of the granular layer of the cerebellum with sparing of the Purkinje cells has been described with gastric, vesical, gallbladder, and pancreatic as well as bronchial and breast carcinoma.[17] These cases, however, include no cerebellar signs, and the changes in the granular layer appear to be a terminal event.

Diagnosis. Visceral carcinoma is probably the commonest cause of cerebellar degeneration seen in a general hospital.[6] In middle life, therefore, the development over the course of a few weeks of bilateral cerebellar signs in the absence of a family history should lead to a careful search for an underlying carcinoma. The condition is distinguished from primary and secondary cerebellar tumor by the absence of increased intracranial pressure and from vascular disease by the subacute course and the absence of other localizing signs. More chronic cases may resemble disseminated sclerosis, particularly when extensor plantar reflexes, brisk tendon jerks, and paretic colloidal gold curves are present and when there are fluctuations in the severity of the symptoms. The presence of other systemic diseases such as myxedema, tuberculosis, syphilis, and uremia will be detected by the appropriate clinical and laboratory features. Extrinsic causes such as lead and organic mercurial poisoning and previous trauma and heat stroke may be excluded by the history. Very rarely, subacute cortical cerebellar degeneration, both sporadic[18,19] and familial[20] may occur independently of other disease.

Management. Treatment should be directed primarily toward the underlying tumor. Although its successful removal may result in a complete remission of cerebellar symptoms,[9] this is exceptional. Treatment is otherwise symptomatic.

Pathogenesis. That cerebellar neurons are particularly sensitive to inimical agents is well known. Purkinje cells particularly are affected with hypoxia,[17] heat stroke,[21] and, occasionally, visceral carcinoma.[6,10,15,16,22] The granule cells are damaged by hypoglycemia,[17] uremia,[23] chronic alcoholism,[24] lead poisoning,[25] and, sometimes, visceral carcinoma.[17,23] Both granule and basket cells may be affected in intoxication with organic mercurial compounds.[26] The reasons for this susceptibility are unknown. The principal theories that have been put foreward to account for the association of cerebellar degeneration and carcinoma are:

Intoxication by tumor products.[27] The rarity of cerebellar degeneration in comparison with the commonness of the tumors with which it may be associated, together with the lack of correlation between tumor size and occurrence of cerebellar degeneration,[6] make it unlikely that simple intoxication is responsible.

Sensitization of cerebellar cells to tumor

products has been suggested,[6] but there is no direct evidence of this. An allergic mechanism might be suported indirectly by the raised gamma globulin in the present case, and the occurrence of mononuclear perivascular cuffing in the central nervous system is consistent with such a process.

Virus infection. Perivascular cuffing has suggested to some that a viral infection may play a part in the development of the syndrome.[6,11] Again, there is no direct evidence of this, although the onset of ataxia after an influenza-like illness in the present case is suggestive. Cuffing has been regarded as secondary to local neuronal degeneration,[10,22] but its occurrence in some cases in otherwise normal sites implies some additional process.[11]

Endocrine abnormalities have been present in several cases of carcinomatous neuromyopathy. Myxedema occurred in 3 of Brain and Henson's[6] cases (2 of encephalomyelitic neuropathy and 1 of myopathy). The present patient had a colloid nodular goiter but was not obviously myxedematous. It is interesting that cerebellar symptoms occurring with myxedema (sometimes unsuspected) have been well described recently.[28] Many patients with carcinomatous neuropathy, however, have no endocrine disturbance.

Some evidence exists for *competition between tumor cells and normal cells for metabolites* as the mechanism in cachexia.[29] A similar process may be involved in the pathogenesis of cortical cerebellar degeneration,[6] but there is as yet insufficient information about the biochemical and ultrastructural characteristics of cerebellar neurons and ovarian carcinoma cells to say how this might occur.

Hereditary predisposition. The suggestion that adjuvant factors might play on a cerebellum with an inherent tendency to degenerate is rather unlikely because of the usually different distribution of lesions in carcinomatous cortical cerebellar degeneration and the hereditary ataxias.[22]

Support for any of these theories is insufficient to provide a satisfactory explanation of the association of carcinoma and cortical cerebellar degeneration. It is clear that development of the syndrome depends on the addition of some other disorder—perhaps allergic, infectious, endocrine, or hereditary—to the simple effects of the tumor.

SUMMARY

A case of subacute cortical cerebellar degeneration secondary to carcinoma of the ovary is presented. The chief clinical and pathologic features of the syndrome are described. The subacute development of bilateral cerebellar symptoms in a middle-aged person in the absence of a family history of cerebellar degeneration should lead to a painstaking search for an underlying carcinoma. Treatment is directed toward the underlying tumor and to the relief of symptoms. The theories of pathogenesis are discussed; none, at the present time, is completely satisfactory.

The author is indebted to Dr. F. O. Bennett for his permission to publish, to Dr. C. T. Jones for access to his notes, and to Dr. D. T. Stewart for making the pathologic material available.

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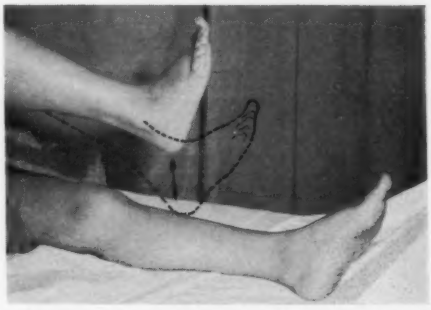
An improved test of motor coordination in the lower limbs

C. M. Fisher, M.D.

APART FROM OBSERVATIONS of stance and gait, motor coordination in the lower limbs is commonly tested by having the patient perform one or more standard maneuvers: holding the legs extended, running the heel of one foot down the shin of the other leg, raising the extended leg to touch the examiner's finger with the great toe, wiggling the toes rapidly, rhythmically tapping the toe or the heel on the floor, alternately drawing the limb up in full flexion and then extending it, executing a circular movement in the air with the toes pointed, and making cycling movements. The purpose of such tests is clearly twofold: first, to detect an abnormality not otherwise evident and, second, to assist in analyzing the nature of an obvious abnormality in terms of its various components—cerebellar, pyramidal, extrapyramidal, and so forth. Not always satisfied with the information gleaned from the above battery, the author has tried out several other coordinated actions. The test pictured in the figure has proved to be of considerable help in both detecting and assessing a motor disturbance. In the test—called "shin-tapping"—the patient is asked to tap the heel of one foot lightly and rapidly, 7 times or so, on the upper part of the shin of the other leg. Instructions for the test are easily understood, and the examiner can indicate with his finger the spot to be tapped, about 2 to 3 in. below the tibial tubercle. The patient customarily keeps his eyes open and observes what he is doing. The heel is raised 4 to 5 in. each time, and the ankle of the tapping foot is kept dorsiflexed to add to the accuracy of the test. Normally, the maneuver is easily carried out with precision, fluency, and rhythmicity at a rate of approximately 2 to 3 per second, even



To test motor coordination in the lower limbs, the patient is instructed to rapidly tap the heel of one foot on the upper part of the shin of the other leg.

in patients aged 70 or over; the nondominant limb is usually less dextrous than the dominant. Some patients in a supertest of coordination have held the target leg off the bed while tapping with the heel.

When used in conjunction with two or more of the usual tests, shin-tapping provides useful confirmation of the presence or absence of an abnormality of coordination, but of more practical importance is the fact that, on many occasions, the test has either been positive when the others were negative or has drawn attention to a mild deficit which would have otherwise been overlooked. In all but a few patients, shin-tapping has been more strikingly positive than the heel-knee-tibia or toe-finger test, and in no instance was the former negative when the others were positive. Thus, it is useful as a screening test, especially if precision is insisted upon and abnormal slowness

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is not overlooked. Shin-tapping has an advantage over the toe-finger test in that weakness of the hip-flexors interferes less and, if necessary, the thigh may be supported while tapping is carried out.

Of the several disorders of motor incoordination, the test is probably most sensitive to cerebellar deficit, and dysmetria, overshoot, undershoot, and "hold-up" can be observed with striking clarity. Pyramidal disease leads chiefly to slowness and small excursion, but, as speed of movement is encouraged, "hold-up" and dysmetria may occur, making it difficult to decide if the disturbance is cerebellar or pyramidal or a mixture of the two. With extrapyramidal disease, the test is carried out slowly and with gradually diminishing excursion. However, as already stated, the chief value of the test is in the detection of minor disturbances in early disease, in which respect the heel-knee-tibia test particularly is often unsatisfactory.

Association of behavior disorder with an electroencephalographic focus in children without seizures

Lt. Joseph B. Green, M.C., U.S.N.R.

THE PURPOSE of this communication is to report a series of 10 children who had abnormal electroencephalograms characteristic of the interictal epileptic state but who had not had any recognizable type of epileptic seizure at the time of initial study. These 10 were selected from a group of one hundred and thirty children, all of whom had been referred for study and electroencephalograms because of behavior disorder or suspected mental retardation. In many cases, the referral was initiated by a school psychologist after testing suggested an "organic" mental disorder.

All electroencephalograms were performed with a standard Grass 8-channel machine. No sedation or activation technics other than spontaneous sleep were employed. The children were followed for periods up to two years in the Pediatric Neurology Clinic of this hospital. Anticonvulsant drugs were prescribed for all children, and clinical observations of the effect of this therapy were recorded. The children, because of similarities in clinical features, were divisible into 3 groups, and their case histories, which follow, will be so arranged.

CASE REPORTS

Group I: Hyperactive children with short attention span and (probable) intellectual deficit

Case 1. P. S., an 8-year-old boy and only child, was seen in consultation because of hyperactive and destructive behavior. Prenatal course and delivery had been uneventful. Growth and development during the first six years had been normal; there had been no significant illnesses. Coincident with his enrollment in school, the child was noted to be hyperactive, with a short attention span. He was incapable of sustained effort. He had frequent temper tantrums and was expelled from school because he would not obey the teacher and disrupted the classroom activities. Psychologic testing revealed a resultant IQ of 78 (Stanford-Binet). The results of the subtests were uniform.

Physical examination revealed a well-developed but hyperactive child, who appeared alternately aggressive and fearful. No abnormalities were noted on the neurologic examination. Roentgenograms of the skull were within normal limits. An electroencephalogram revealed a well-organized waking record with a dominant frequency of 10 cps. During drowsiness and light sleep, frequent biphasic spikes were seen in the left temporal derivations (Fig. 1). Reinterrogation of the parents disclosed no family history of convulsive disorder, nor had the child had any disturbances of consciousness. Dilantin, 100 mg., was instituted twice daily. According to his mother, he was less hyperactive while on this medication. After one year of therapy, the drug was suddenly discontinued. About twenty-four hours later, he had a grand mal convulsion.

Case 2. P. D., a 7-year-old boy, was seen because of behavioral difficulties at home and school. He was described as hyperactive and destructive, and he seemed to "hate everybody." He would not mind at school and was dismissed. He had injured several children. His mother described him as "high strung" and "in a world by himself." He had no staring spells or convulsive seizures. He seemed a normal child in all respects until one year before this initial interview. The behavior problems were first noted after a move of the family. The prenatal period was unremarkable, and delivery was full-term and normal. He walked at 1 year and spoke sentences at 2 years of age. There were no significant illnesses other than

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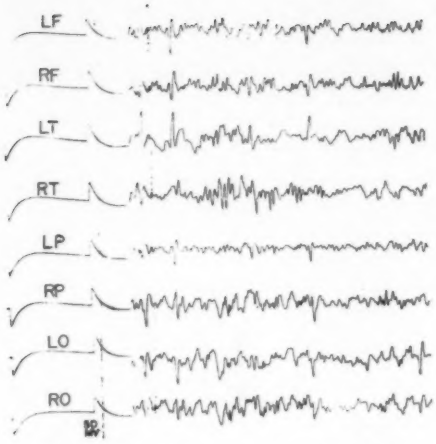

Fig. 1. *(Case 1)* Monopolar recording referred to both ears. Note left temporal spikes with reversal in other leads. Light sleep

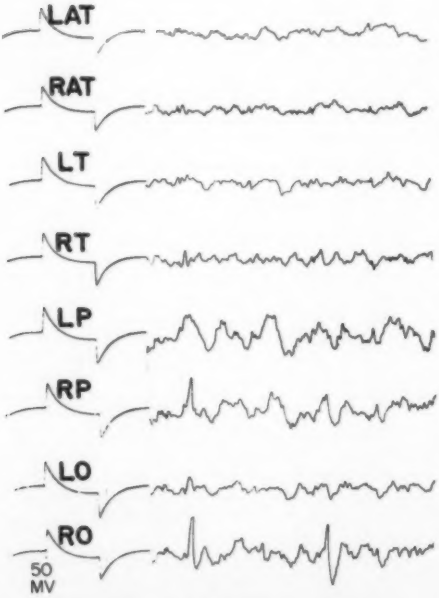

Fig. 2. *(Case 2)* Monopolar recording referred to both ears. High voltage spikes are present in right occipital. Drowsiness

rubella, which had a benign course. Family history was negative for convulsive disorder.

Physical and neurologic examinations were within normal limits. The child was uncooperative and hyperactive. Attention span was very brief, and he could be made to complete simple tasks only with constant urging. Roentgenograms of the skull were unremarkable. An electroencephalogram revealed a well-organized, mature waking record, but, during sleep, biphasic spikes were present in the right occipital lead (Fig. 2). The child was placed on Dilantin, 100 mg., nightly. This was later increased to 100 mg. twice daily. He was followed for six months, and no improvement was noted in his behavior.

Case 3. R. C., an 8-year-old boy, was referred because of a poor adjustment to school. His attention span was very short. He was extremely "nervous" and excitable. He failed to relate to other children and entered games only when compelled to do so. He had difficulty in writing, drawing, cutting with scissors, and other manual tasks. He was obedient and waited on his teacher, helping to clean the room, pick up papers, and put books away. His mother felt he was very clumsy and incoordinated. He was the only child of a second marriage and had 2 (maternal) siblings aged 18 and 19.

The prenatal history was unremarkable. Delivery was full-term and normal in all respects. Growth and development was normal; he walked at 1 year and spoke sentences at 3 years of age. However, a noticeable lisp persisted. He had had no significant illnesses. He spent two years in kindergarten because of "immaturity." A Stanford-Binet test administered at age 6 scored an IQ of 63. He had had no convulsions, syncope, dizziness, or staring spells. The family history was negative for seizures.

Physical examination revealed a shy and fearful child who lacked confidence in his ability to perform the simplest tasks. Digital tasks were performed poorly, but no gross incoordination was present. Simple commands had to be repeated several times. Roentgenograms of the skull were within normal limits. An electroencephalogram contained frequent biphasic spikes localized to the right occipital lead (Fig. 3). The child was started on Dilantin, 150 mg. daily. Coincident with this therapy, he was observed to relate better to other children, and he became more aggressive in his interpersonal relationships. No improvement in learning ability was noted.

Case 4. J. L., a 13-year-old boy, was referred because of school problems. He had been seen in the Neurology Clinic five years before and had been placed on Dilantin at that time because of an abnormal electroencephalogram. He had never had a convulsion, however. The prenatal history was unremarkable. Delivery had been normal and full-term. He had been a colicky baby, but weight gain was normal. Although he walked at the age

of 15 months, he stumbled a great deal and, according to the mother, was always poorly coordinated. He spoke sentences at 3 years of age, but speech remained indistinct for many years. He had both rubeola and varicella when 3 years old; these illnesses were mild.

From the ages of 3 to 5 years, he had frequent temper tantrums. In kindergarten, he was hyperactive and noisy and failed to play with other children. When he entered the first grade, it was noted that he had a short attention span, "couldn't concentrate," and failed to learn. Since that time, he had been in special classes. He did "better" when given individual instruction and when he did not have to compete with other children. He learned to read acceptably but did poorly in arithmetic. A Stanford-Binet revealed an IQ of 72, with uniform results in the subtests. Family history was significant in that he had a brother, aged 10, who was hyperactive and a poor learner. An aunt had congenital blindness and convulsions.

Repeated neurologic examinations were within normal limits. Several electroencephalograms were similar. Spike discharges were seen in the right temporal, parietal, and occipital leads (Fig. 4). His mother stated that he was less hyperactive and concentrated better when he took Dilantin. When the drug was replaced by a tranquilizer, his behavior and ability to learn definitely deteriorated.

Case 5. C. D., a 5-year-old boy, was referred because of mental retardation; at birth, "club" feet and a "short neck" had been noticed. Delivery had been unremarkable except for ruptured membranes twelve hours before delivery. He gained weight slowly and was prone to frequent respiratory infections with high fevers. A heart murmur was heard at age 3 weeks but eventually disappeared. He did not walk until the age of 2 and, at the age of 5, did not speak sentences. His comprehension of speech was good. Vocabulary was limited to a few words. There were no behavior problems. He had had no serious illnesses, convulsions, or syncope. Family history was negative for convulsive disorder.

Physical examination disclosed an undersized child with exceptional muscular development. He was clumsy in the performance of digital movements. He was unable to pronounce consonants, all attempts at speech ending in vowel sounds. The child was easily distracted. The metatarsus varus present at birth had been corrected. Gait was normal, with no suggestion of spasticity. Roentgenograms of the skull were within normal limits. An electroencephalogram revealed spikes in the left occipital (Fig. 5). The child was placed on Dilantin, 100 mg. daily. No change in mental status or behavior was observed.

Group II: Children of normal intelligence with varied behavioral problems

Case 6. E. D., an 8-year-old girl, the second of 3 siblings, was referred because of enuresis. The

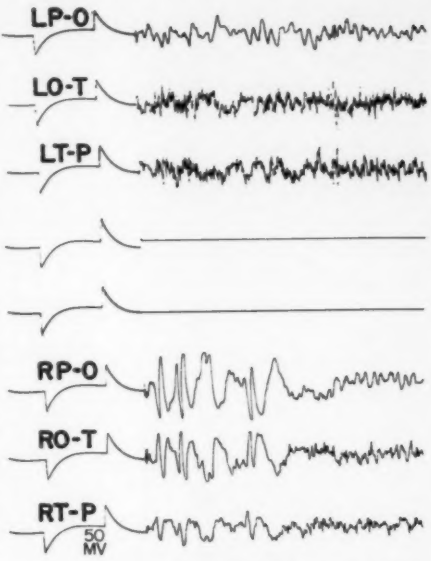

Fig. 3. *(Case 3)* Triangulation (posterior). Spikes and slow waves with reversal, right occipital focus. Artifact due to muscle discharge.

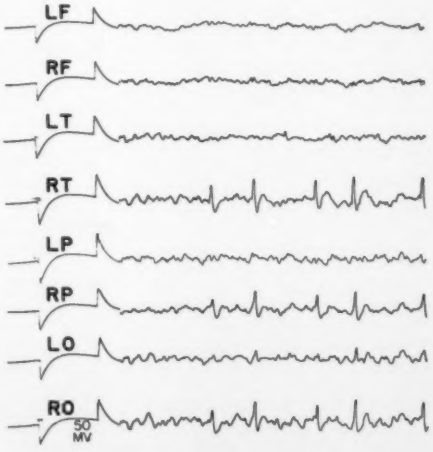

Fig. 4. *(Case 4)* Monopolar recording referred to both ears. Frequent spikes are present in right temporal, parietal, and occipital leads. Drowsiness

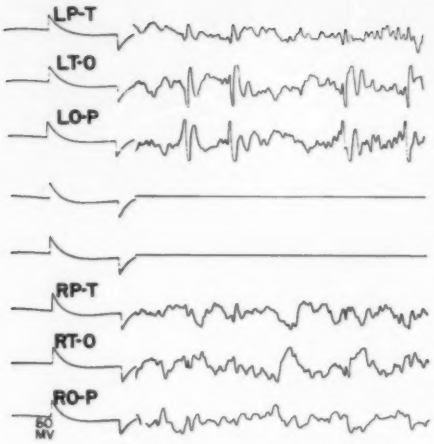

Fig. 5. *(Case 5)* Triangulation (posterior). High voltage biphasic spikes with reversal. Left occiptal focus. Sleep

prenatal history was significant in that the mother had mild toxemia and suffered headaches and visual disturbances through the last trimester. The child was born at full-term under spinal anesthesia and appeared to be in good condition at birth. She gained weight and developed normally, walking at 10 months of age. Past medical history revealed that at the age of 3 years she fell, striking her head and losing consciousness. Recovery was rapid, and no skull fractures were sustained. At the age of 5, she had mild cystitis.

She had always been an aggressive, confident child. During the year before medical aid was sought, the mother noticed the following personality changes. The child appeared quiet, appeared to lose interest in play with other children, and cried easily. Enuresis became frequent. Extensive questioning failed to reveal any evidence of convulsions, automatic behavior, or lapses of consciousness. Psychologic testing had been performed, and the result of a Stanford-Binet test was an IQ in the normal range but with considerable scatter of the test results.

Neurologic and general physical examinations were entirely within normal limits. The child appeared poorly related and frightened, despite frequent reassurance. Roentgenograms of the skull were within normal limits. An electroencephalogram was obtained, and the waking record was well-organized, with a dominant frequency of 8 cps. During drowsiness and light sleep, frequent biphasic spikes and spike-and-wave complexes were present in the right middle temporal leads and occasionally were seen in both temporal derivations (Fig. 6). The child was placed on Dilantin, 100 mg. twice a day. On the third day of this medication, the mother noted that the child was more related and much more aggressive and that the enuresis had ceased. On the eighth day of anticonvulsant medication, a generalized macular rash appeared and the Dilantin was suddenly discontinued. Approximately twenty-four hours later, the enuresis had recurred and the child once again appeared withdrawn and fearful. Mysoline therapy was then instituted, 125 mg. twice daily. On the second day, the enuresis ceased and the improvement seen with Dilantin recurred. The child was maintained on Mysoline for ten months, during which period a definite personality change was noticed, with an increase in spontaneity, aggressive behavior, and general relativeness.

Case 7. S. S., a 4-year-old boy, was referred to the Clinic because of behavior problems. Prenatal history was noncontributory, except for a mild flu-like illness occurring during the fifth month. Labor was of normal length, but there was some delay in the initiation of respiration. The child was kept in the hospital eight days. He was mildly jaundiced on the second day; no blood-type incompatibility was discovered. He gained weight and developed "normally." He walked at the age of 1 year and spoke a few sentences at the age of 18 months. He had had no important illnesses. His mother sought help because of increasingly destructive behavior, cruelty to other children, and temper tantrums. At times, he ap-

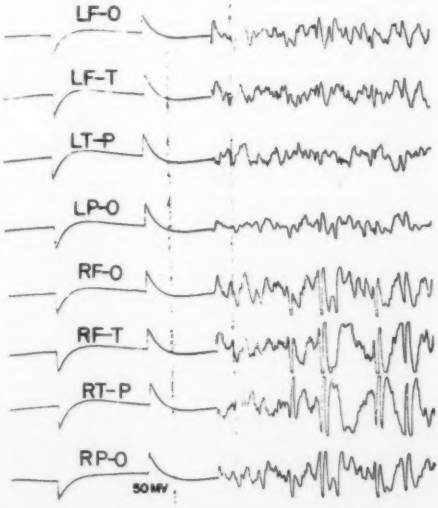

Fig. 6. *(Case 6)* Bipolar recording. High voltage discharges appear best localized to right temporal but are not confined to this lead. Drowsiness

peared preoccupied, humming to himself and refusing to play. At all times, however, his attention could be secured. He displayed insight into his behavior by asking his mother, "Why am I so mean?"

These patterns of behavior worsened periodically, being most marked for three or four days, after which improvement occurred. He had had no convulsions, even with high fevers, staring spells, or irrelevant automatisms. There was no family history of convulsive seizures.

Neurologic and general physical examinations were entirely within normal limits. Although responding to commands, the child appeared withdrawn, preoccupied, and disinterested in his environment. Ophthalmologic examination revealed organically normal eyes and adnexa, but hand-eye coordination and binocularity were below the expected level of performance for his age. Routine laboratory studies and roentgenograms of the skull were within normal limits. Psychologic testing revealed intelligence in the superior range (Stanford-Binet). There was a disparity between intellectual abilities and (deficient) performance skills. An electroencephalogram revealed a well-organized record with frequent spikes in the right temporal leads (Fig. 7). Therapy with several anticonvulsants had little, if any, effect on his behavior patterns.

Case 8. W. C., a 7-year-old boy, was referred because of "school problems." According to his teacher, he was destructive and aggressive, having injured several classmates. He could not attend well, and his memory was poor. He showed no interest in schoolwork and was described as a child who seemed to hate the whole world. He complained frequently of headache. Nightmares were common. He had no convulsions, automatisms, syncopal episodes, or staring spells. His mother had recently been hospitalized because of an acute psychotic break during which she had threatened to kill him and his younger sister. At the time of initial examination, he was living with a grandmother.

Family history, insofar as could be determined, was negative for convulsive disorder. The prenatal history was unremarkable. Delivery was at term and normal. Development was normal; he walked at 11 months and spoke sentences at 2 years of age. He had measles at 3 years, shortly followed by varicella. About this time, he had another febrile illness of obscure etiology; further details were not available. Behavioral difficulties were not prominent until he started school.

Neurologic and general physical examinations were within normal limits. The boy related readily and was well-coordinated. Intelligence was estimated to be in the normal range. Roentgenograms of the chest and skull were within normal limits. An electroencephalogram revealed bursts of spikes in all leads followed by high-voltage slow waves, 3 cps (Fig. 8). This abnormality

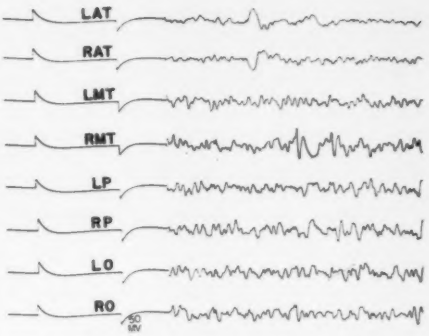

Fig. 7. *(Case 7)* Monopolar recording referred to both ears. Spikes are present in right middle temporal lead. Sleep

occurred only during sleep. Dilantin, 100 mg. nightly, was instituted. Coincident with this, there was a remarkable improvement in his behavior; he became tractable and made a good school adjustment, a fact confirmed by his teacher.

Group III: Children with paroxysmal headache associated with behavioral abnormalities

Case 9. K. H., a 9-year-old girl, was referred because of headaches. These had been present for

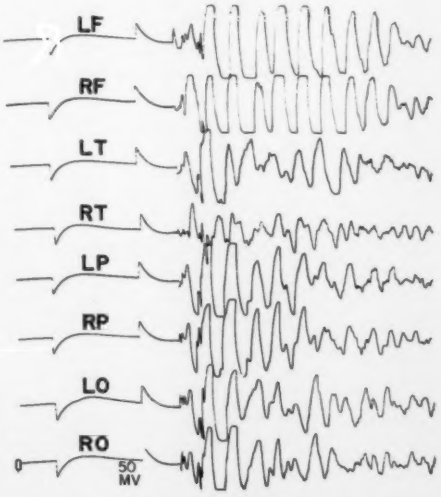

Fig. 8. *(Case 8)* Monopolar recording referred to both ears. Spikes followed by high voltage slowing. Sleep

the past four years, and were associated with vomiting. Headache was paroxysmal, with sudden onset and no localization. The attacks lasted for several hours and were concluded with vomiting. She also complained of occasional "dizziness," and her mother noted increased irritability. Although of normal intelligence, as determined by psychometric testing, she did poorly in school because of inattentiveness. She "didn't seem to try." She had had no staring spells or convulsive seizures. Before, during, and after a headache, she responded readily and was in good contact.

Prenatal history was noncontributory. After a normal full-term delivery, she gained weight rapidly and developed normally. She walked at the age of 1 year and was speaking sentences at the age of 2. When she was 15 months of age, she contracted a febrile illness and slept continuously for five days. At 4 years of age, she fell, striking the occiput. She did not lose consciousness but slept a great deal for a few days after this injury. Family history revealed an aunt who had "migraine" which began at the age of 9 years.

Neurologic and general physical examinations were within normal limits. The child appeared alert and friendly. Roentgenograms of the skull and chest were within normal limits. An electroencephalogram revealed a normal waking record, but, during sleep, spike discharges were present, sharply localized to the left occipital lead (Fig. 9). Dilantin, 100 mg. nightly, was instituted.

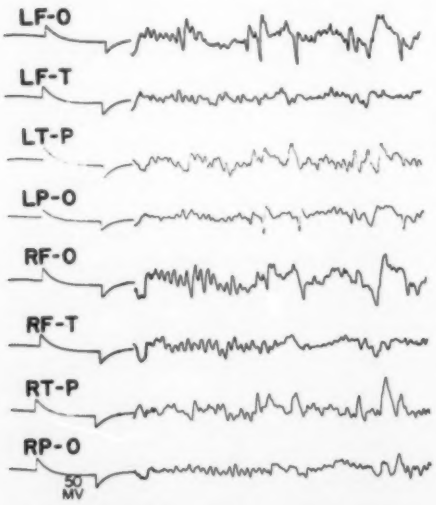

Fig. 9. *(Case 9)* Bipolar recording. Spikes in leads having a left occipital component. Spikes were biphasic in monopolar derivations. Sleep

During six months of this therapy, she had no headaches. This represented a change, for she usually had at least two headaches a month. She also did much better in her school work.

Case 10. T. R., a 6-year-old boy, was referred because of headaches and behavior disorder. The headaches were bifrontal and associated with pupillary dilation, increased sweating, and shivering. He had had no abdominal pain. During these attacks, of which there were several a month, he remained in good contact with his environment and responded readily. This was confirmed by a personal observation of the child during a headache. His behavior was inconsistent; he was alternately destructive and ingratiating. On several occasions, while on early morning forays, he emptied the refrigerator of its contents, dashing all of the eggs to the floor. He had spells of "day-dreaming" but always responded readily. His performance at school was also inconsistent, but he had shown himself capable on a few occasions of superior work. However, he required frequent disciplinary action.

He was the second child of an RH-negative mother. He was born prematurely at six months' gestation and weighed a little over 2 lb. at birth; 3 to 4 small transfusions were administered during the immediate postnatal period. He was discharged to home after four months' hospitalization. He walked at 18 months and spoke sentences at age 3 years. He had a "viral" diarrhea at the age of 1 year but no other remarkable illnesses.

Physical examination revealed a friendly child, alert and well-coordinated. No abnormalities were noted on neurologic examination. Roentgenograms of the chest and skull were within normal limits.

An electroencephalogram contained frequent biphasic spikes, limited to the left temporal and occipital leads (Fig. 10). Mysoline, 250 mg. daily, was started. On follow-up visits over a period of nine months, his mother resported only 2 headaches and a remarkable improvement in his behavior. He was no longer destructive, and his teacher confirmed the fact that his school work was consistently good, with no disciplinary problems. He seemed a normal boy in all respects.

DISCUSSION

The 5 children in Group I were remarkably similar in respect to intelligence, behavior, and electroencephalographic findings. Slight to moderate intellectual deficit, hyperactivity with inability to concentrate, and a temporal or occipital spike focus were common to the group. Various potential causes for this syndrome could be cited in individual cases, including birth trauma, heredity, blood-type incompatibility, and obscure febrile illnesses, but a distinctive or uniform etiology was lacking.

Glaser and Dixon,[1] in reporting interseizure manifestations of children with psychomotor epilepsy, described impulsive, aggressive, hyperactive behavior as a "common denominator." Psychometric tests performed in 12 of their patients revealed an intellectual deficit in 6, with intelligence quotients ranging between 70 and 80. A striking similarity exists between the interseizure manifestations of children with psychomotor epilepsy, as noted by Glaser and Dixon, and the characteristics of our Group 1 children with no history of seizures.

The psychiatric characteristics of the Group II children were varied and included oscillations in behavior, a degree of autism, and in each case normal or superior intelligence. Nightmares, inability to relate to other children or teachers, and hostile destructive behavior were among the prominent disturbances. Such changes were also encountered by Glaser and Dixon in their study of epileptic children.[1] After comparison of the clinical features of our Groups I and II with the interseizure manifestations of children with psychomotor epilepsy, reported by Glaser and Dixon and others,[2] the only differences ascertained were the absence of identifiable seizures in our series and the predominance of an occipital, rather than a temporal electroencephalographic focus. It may be postulated that a more posterior focus reduces the tendency to overt seizures, while still associated with behavioral abnormalities observed with an anterior temporal lesion. That a definite potential to seizures is present with a temporal focus was demonstrated in the case of P. S. (Case 1), who had a generalized convulsion after a year of observation.

It is possible that the behavioral abnormalities of the children currently reported represent a preictal syndrome and that most, if not all, of these children will eventually have a convulsive disorder. Against this hypothesis is the history of J. L. (Case 4), who after a five-year period of observation still was seizure-free. He had, however, received anticonvulsant medication for most of this time. Long-term observation of these children should better determine if their symptomatology does indeed constitute a preictal state.

The results of anticonvulsant medication in respect to the amelioration of behavioral abnormalities were, with a few exceptions, disappointing. In most cases, any improvement observed could be attributed to an increase in parental understanding of the child's problem coupled with a reduction in guilt feelings. It is thought that in Cases 6 and 8 such factors were not an adequate explanation for the improvement noted and that anticonvulsants were of definite benefit. These observations in general tend to support the concept of Gibbs[3] that electrical abnormalities may serve to locate the anatomic substratum of psychiatric disorders in epileptic patients but are not of themselves causative factors.

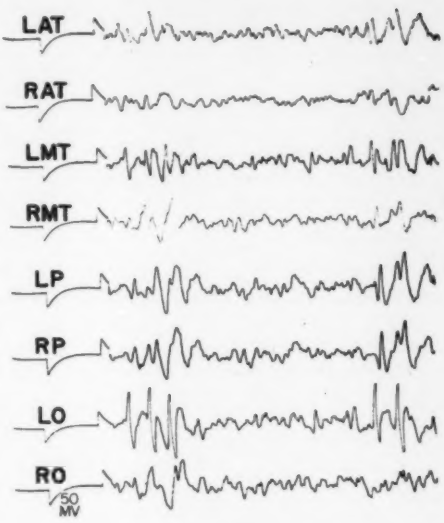

Fig. 10. *(Case 10)* Monopolar recording referred to both ears. High voltage biphasic spikes best seen in left occipital. Drowsiness

The excellent response of the 2 children of Group III to anticonvulsant therapy is worth emphasis. These 2 cases were distinguished by severe paroxysmal headache and autonomic reactions, such as vomiting, pallor, and sweating. These attacks appeared to represent epileptic cephalgia, or epileptic equivalents, as recently described by Halpern and Bental.[4] The reason for the response of the accompanying behavior disorder to therapy is not clear, since this did not appear to be an ictal phe-

nomenon of the type described by Goldensohn and Gold.[5] These authors reported individuals subject to prolonged abnormal behavior accompanied by bilaterally synchronous paroxysmal activity in the electroencephalogram. Our patients were distinguished from such cases by the absence of alteration of consciousness and the presence of a cortical electroencephalographic focus.

SUMMARY

Behavior disorders associated with abnormal electroencephalograms in 10 children are reported. A spike focus in a temporal or occipital area was identified in all but one case. None of the children had a history of seizures at the time of initial study.

These children were strikingly similar in behavioral characteristics to children with psychomotor seizures. Anticonvulsant medication was prescribed in each case, and the effect of this therapy upon the behavior disorder was evaluated.

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Seizures associated with the Catlin mark

William C. Kite, Jr., M.D.

THE PRESENT CASE is being recorded here for two reasons: first, because there does not seem to be documentary proof that "fenestra parietalia symmetricae" could be associated with epilepsy and, second, because no patient possessing this hereditary congenital deformity has been reported to have had surgical exploration during life.

The term, Catlin mark, seems to be a justifiable name for these windows in the parietal bone, since it connotes the only thing about these curious openings of which we can be sure, that is, their familial distribution. The name "foramina parietalis permagna"[1] has been applied to them by O'Rahilly and Twohig,[2] but it implies that we know why these defects in the parietal bone exist. Pepper and Pendergrass[3,4] also imply that we know that these openings in the parietal bone are actually defects in ossification about the parietal emissary foramina. The facts are that certain patients have been reported with huge symmetric skull defects in the parietal region and also with normal parietal emissary foramina medial to the defects.[5] That these defects are in a general zone between the two ossification centers of the parietal bone seems clear and that in the embryo a cleft in this general region can be encountered routinely at certain stages is also without doubt, but there is nothing in either the embryo or the adult to indicate why such huge defects in the parietal region of the skull exist.[5] The term, "enlarged parietal foramina," employed by Pepper and Pendergrass,[3] has the same drawback in that we cannot be certain these openings are actually failures of ossification about the parietal emissary foramina. Most writers[2,4–7] have been careful to demonstrate the difference between the hereditary openings under discussion here and the normal variations of parietal emissary foramina, which may attain a diameter of 4 mm., and other parietal bone abnormalities, such as a marked thinning of this bone, which may occur as a symmetric deformity on either side of the midline in approximately the same location as the hereditary windows but which are not familial.

Goldsmith[6] has pointed out, as have other writers, that approximately one-third of skulls taken at random show no parietal emissary foramina at all and only approximately one-third show both parietal emissary foramina present. He feels that, while some Catlin mark parietal windows can be found without any evidence of familial involvement and would therefore appear to be a true "sport," they really represent the same hereditary tendency appearing simply in insufficient progeny to demonstrate a clear-cut family history of the mark. The name "fenestrae parietalis symmetricae" coined by Halbertsma[8] has the unfortunate drawback that the openings are not always symmetric.[6] Piersol[5] has also pointed out that arterial grooves in the skull have been found entering the border of the Catlin mark opening, and, therefore, he feels confident that they actually transmit arteries at times. One is left with the conclusion that none of the names thus far proposed is wholly satisfactory, because even Catlin mark refers to a single large collection found in members of the Catlin family and reported by Goldsmith. It certainly was not the first record of familial involvement.

Since Lancisi's first description of these openings in 1707[9] and up to the present time,

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the clinical significance of these openings has been considered extremely meager. The only symptoms associated with Catlin mark deformities are headaches resulting from digital pressure around the opening or from combing the hair over them. A single vague reference to epilepsy by Piersol[5] can be found which states merely that epilepsy was occasionally blamed on the openings. This is not documented in any of the literature.

The first case of bilateral parietal windows described during life was that of Greig,[10] who recorded, "On admission he gave the following history: he stated that he had always enjoyed exceptionally good health, had never had syphilis, and was a total abstainer. His service had extended over five and a half years, four and a half of which had been spent in India. He referred the commencement of his illness to a fall from a horse. The injury did not produce unconsciousness nor necessitate his admission to hospital. Later on he began to have pains in his head, often accompanied by attacks of giddiness. He stated that the attacks came on if the weather was very hot or close, or if he had to remain in one position for a long time, as on parade. An attack of giddiness began with beating in the eyes, accompanied by flashes of light, his whole head swam, and there was frequently ringing in the ears."

Fig. 1. Pneumoencephalogram shows slight enlargement of left ventricle, especially beneath left window.

This recital would constitute a moderately convincing description of a minor seizure problem were it not for the fact that the patient later told Greig he had invented the story from beginning to end by merely following the questions that had been put to him by his various examiners. He had used this as a successful means of malingering for some time until his period of service was over. The fact that digital pressure on the openings when Greig examined him actually produced flashes of light makes one wonder if the original story might not have been true and the patient had decided to deny it for some reason after his discharge from service.

While Hess[11] has pointed out the frequent association of congenital deformity of the nervous system with Wormian bones in the skull, no such connection with any disease has been borne out by the repeated reports of parietal windows, even though Piersol[5] felt that a high proportion of his skulls bearing the mark were microcephalic. Epilepsy is not mentioned specifically in any of these reports. The chief clinical interest has centered upon differentiating these openings from other skull defects, which is easily done from their position, lack of signs of erosion around the borders of the opening, usually symmetric appearance, and, of course, a familial history. Increasing numbers of families affected by the defect have been reported in the recent literature, the largest being the Catlin family, consisting of 57 members spread over 5 generations, with 16 members bearing the mark.[12] In 1895, Symmers[13] was the first to mention a case where the father had the same type of skull defect as the patient, but it was not until later that the true familial character of the mark became evident.

The following is the case history of J.L., a 15-year-old white youth.

The chief complaint was of "seizures and holes in the head." Family history was negative for

convulsions. The mother, 3 uncles, and the grandmother all had bilateral, round skull defects in the parietal region, most of which were about the size of a quarter or smaller. Palpable defects about the size of a nickel were present in the parietal region of the mother. She was unable to recall any member of her family who bore the name of Catlin, and the majority of the family were of French-Canadian stock.

The patient was born at full term after a three-hour delivery with no forceps, and there had been no trouble with respirations at birth. No oxygen had been necessary, and, after birth, there had been no feeding problem in the first two or three weeks. As an infant, he had had an operation for hernia in the left inguinal region.

As long as he could remember, the youth had had intermittent headaches, with appreciable bulging of the defects and occasional vomiting. When the headaches stopped, the bulging ceased. At the age of about 12, the patient noted onset of seizures, which first occurred at the rate of about 1 a month. However, the frequency diminished in the next two years, until he had had only 3 seizures during the year before examination. He had not been taking any medication during that year. The seizures were invariably nocturnal. He awakened with a headache, and the pattern included a choking sound, biting of the tongue, and bilateral, generalized, clonic movements of the limbs; he had no incontinence. The head and eyes remained fixed straight ahead. After the seizure, there was some vomiting and a severe headache with bulging of the 2 soft areas in the skull. More recently, the areas had begun to sink in during part of each day, but usually in the morning they were elevated.

Physical and neurologic examinations were negative throughout except for 2 areas in the posterior section of the skull which were concave, the one on the right being approximately 2 in. in diameter and the other a little smaller. A bridge of bone was palpable between them over the sagittal sinus, and there was no skull bruit.

The patient was admitted to the hospital chiefly because the defects were of such size that he had been prevented from participating in sports at school. It was felt that a methyl methacrylate cranioplasty could solve the sports problem for him and, also, very likely stop the headaches. As it was not clear at the time of examination whether there was a connection between the seizures and the openings, immediately after admission to the hospital an electroencephalogram was made and revealed a left parietal spike focus directly beneath the left opening. Since the bulging of the two openings had been such a prominent feature, a pneumoencephalogram was also made to rule out associated hydrocephalus. This film revealed slight enlargement of the left ventricle, particularly beneath the left window (Fig. 1). Roentgenograms of the skull (Figs. 2 and 3) show the openings which by actual measurement are right, 57 by 43 mm. and left, 52 by 38 mm., the largest skull defects of this kind recorded so far.

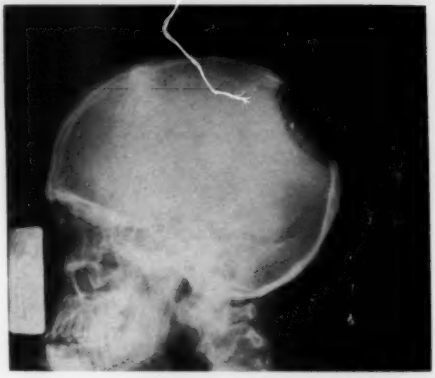

Fig. 2. Roentgenogram shows windows in parietal bone.

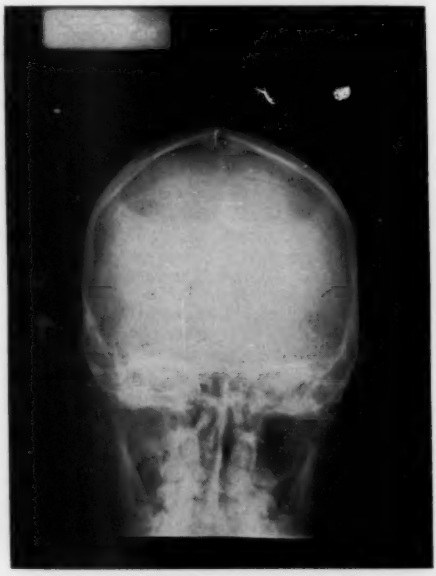

Fig. 3. Roentgenogram shows windows in parietal bone.

At operation, a coronal scalp flap was turned posteriorly, the line of incision being carried across the anterior edge of both openings. Dissection of the bone was dry and normal, but, over the openings themselves, a dense venous network

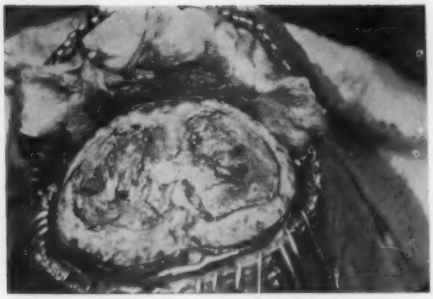

Fig. 4. Scalp flap and periosteum turned back, demonstrating the bony defect and the shaggy vascular tissue which overlie the dura itelf

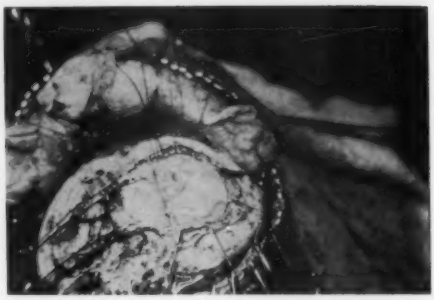

Fig. 5. Thickened dural flap turned back medially from left opening, revealing indistinct enlarged pial vessels in milky pia covering left cerebral hemisphere

was encountered with an occasional small artery in it. One had the impression that the diploic spaces were preserved but that there was no bone surrounding them. The dura over the left opening was then incised and was found to be markedly thickened. At one point in the anterior medial quadrant, a heavy, string-like adhesion between dura and pia was encountered and severed. The pia-arachnoid over the surface of the brain was milky-white and so densely opalescent over at least 50% of the area under the opening that the pial vessels could not be seen through it. No cortical resection was considered at this time because of the relatively minor nature of the patient's seizures. The dura was then closed and a methyl methacrylate cranioplasty fashioned and anchored with stainless steel sutures. The wound was closed with layers of interrupted black silk sutures, and the patient recovered uneventfully. He was discharged nine days later on Dilantin, 100 mg. twice a day. When seen three weeks later, he had had only one very mild headache. He had been playing basketball with success and was otherwise well. It was felt that he should continue with 100 mg. of Dilantin, before retiring, as a permanent medication.

Figures 4 and 5 demonstrate the relative size of the defect at operation and the condition of the surface of the brain. It seems likely that the cortical scarring present here resulted from intermittent mild incarceration of that portion of the brain in the opening at the times when bulging, headache, and vomiting were noted by the patient. In all probability, recurrent venous obstruction at the edges of the opening is responsible for this lesion, which coincides exactly with the patient's electroencephalographic spike focus.

SUMMARY

A review of the literature has failed to reveal a single documented case of parietal windows associated with epilepsy. A report of a patient with the largest openings on record, associated with seizures, is presented. A clear-cut spike focus was found in the electroencephalogram corresponding to a point directly under the left and smaller of the two openings. Surgical exploration performed at the time of cranioplasty revealed meningocortical adhesions and opalescent pia at the site of the spike focus.

A complete bibliography of this subject is available.

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Leukoencephalopathy associated with Hodgkin's disease

C. L. Dolman, M.D., and A. R. M. Cairns, M.D.

PROGRESSIVE multifocal leukoencephalopathy was identified as a separate disease entity and named by Astrøm, Mancall, and Richardson in 1958.[1] They described 3 cases, 2 of which occurred in conjunction with chronic lymphatic leukemia and 1 with Hodgkin's disease. They found 5 other reports in the literature in which the lesions had been diagnosed variously as "unclassifiable," Schilder's diffuse sclerosis, and Hodgkin's disease of the brain. In 3 of these, they were able to examine the slides and thus to confirm that they were identical pathologically with their own cases. Since then, 3 further patients have been reported,[2,3] making a total of 11 cases. The associated disease was in 4 intances Hodgkin's disease, in 3 chronic lymphatic leukemia, in 1 giant follicular lymphoma which had turned into lymphosarcoma, in 1 sarcoidosis, and in 1 pulmonary and renal tuberculosis; in 1, no general illness was mentioned. The associated disease had been present six months to sixteen years previously, and the neurologic illness, which always terminated fatally, had a duration of one month to one year, with the majority falling into the four- to six-months range. The symptomatology was variable, depending on the anatomic sites involved. In all brains, the cerebral hemispheres were affected, which, in 8 of the 11, was more marked in the posterior half, with frequent foci in the basal ganglia. The brain stem was involved in 6 cases and the cerebellum in 3, but extensively so in only 1 case. The foci varied from small lesions to large, confluent, soft, granular areas in the white matter.

The case to be presented here is another typical example of this illness.

CASE REPORT

Clinical summary. The patient was a 51-year-old Venetian-blind manufacturer. At the age of 38, he had noted enlarged lymph nodes in the left groin, which on biopsy proved to be due to Hodgkin's disease. They resolved with local radiation. He remained well during the ensuing thirteen years, although he did have occasional episodes of fever and intermittent enlargement of axillary nodes which always receded spontaneously.

When he was seen at the British Columbia Cancer Institute on December 21, 1959, a supraclavicular lymph node biopsy demonstrated Hodgkin's sarcoma. Two days later, he was admitted to the Vancouver General Hospital after expressing intent of suicide. The patient's wife stated that he had shown mental deterioration in the three months before his admission. Physical examination revealed a generally ill, wasted, pale man who had transverse banding of his fingernails and generalized superfical lymphadenopathy, the largest lymph nodes measuring 7 cm. in diameter. Enlarged abdominal paraaortic lymph nodes were palpable; his spleen was enlarged to 8 cm. below the left costal margin and his liver to 9 cm. below the right costal margin. Otherwise, examination of his chest, cardiovascular system, and abdomen revealed no abnormalities. His blood pressure was 165/85 and his pulse, 90 per minute and of regular rhythm.

Neurologic examination revealed grossly defective perception, attention, orientation for time, and memory for recent events. He had left homonymous hemianopsia, a depressed left corneal reflex, left facial weakness, a depressed left gag reflex, deviation of the palate to the left, and dysarthria. He had severe, left-sided limb ataxia. Motor power was

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generally reduced, in keeping with the severe degree of generalized muscle wasting. No localized motor weakness was found. The deep tendon reflexes were normal; the right plantar response was downgoing and the left, equivocally upgoing. Lack of cooperation made sensory evaluation impossible. Fundoscopic examination showed only moderate arteriosclerosis of the retinal arteries.

Investigation revealed normochromic, microcytic anemia, with a hemoglobin of 7.4 gm. The total white blood count was 3,100 per cubic millimeter, with a normal differential count. The platelet count was 216,000 per cubic millimeter. Prothrombin activity was 100% of normal; nonprotein nitrogen, 32 mg. per cent; and the VDRL reaction, negative. Lumbar puncture showed a clear, colorless fluid under normal pressure. The cerebrospinal fluid contained 6 white blood cells and no red blood cells per cubic millimeter and had a total protein content of 50 mg. per cent. Skull and chest roentgenograms were entirely normal; in particular, there was no enlargement of hilar lymph nodes and no evidence of raised intracranial pressure.

The patient was given several antibiotics but had a constant low-grade fever during his entire hospital stay of forty-six days. Forty-five days before death, he was given a single exposure of 800 rads to his right supraclavicular area; fifteen days later, 0.4 mg. of nitrogen mustard per kilogram was administered intravenously over a two-day period. This therapy was followed by some decrease in the degree of generalized lymphadenopathy, but his course in the hospital was steadily downhill, to extreme emaciation, dehydration, and death on February 4, 1960.

During his hospitalization, his neurologic deficit increased so that within a month of admission he was completely unable to communicate and lay in bed moaning with head and eyes turned to the right, moving only his right extremities. Left homonymous hemianopsia persisted, left facial weakness increased, palatal movement was lost, swallowing became extremely difficult, and complete flaccid left paraplegia with upgoing plantar response as well as right spastic paraparesis with normal plantar response appeared. At no time was there evidence of increased intracranial pressure. Basilar artery insufficiency due to Hodgkin's involvement of the dura was suspected clinically.

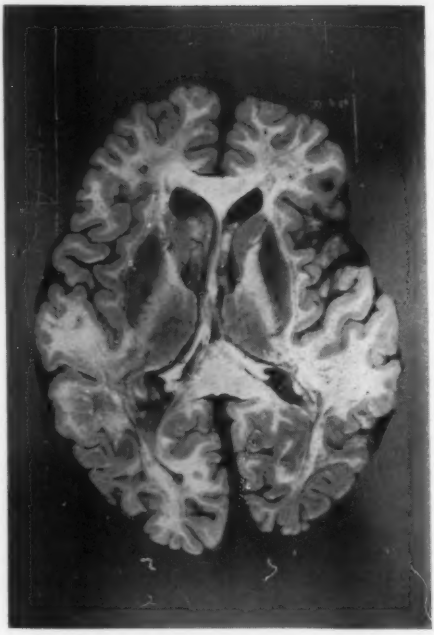

Fig. 1. Upper half of cerebral hemisphere. Visible are a large grayish area in the right parietal white matter, a collapsed lesion in the left occipital lobe, and smaller lesions in the frontal lobes.

Necropsy. The body was severely emaciated. The lymph nodes in the neck, axillae, groins, and paraaortic areas were found to be enlarged 2 to 4 cm. in diameter but on microscopic examination showed only extensive fibrosis without evidence of remaining tumor. The spleen, which grossly was slightly enlarged, contained small foci of fibrosis. Actually, no viable Hodgkin's tissue was found anywhere in the body, with residual lesions only in lymph nodes, dura, and spleen. The cause of death was bronchopneumonia.

In the brain, the basal cerebral vessels were moderately sclerotic but otherwise normal. The dura mater contained over the vertex 2 small, flat, thickened areas which microscopically demonstrated scar tissue with some lym-

phocytes, similar to the lesions in the lymph nodes. Foci of degeneration were scattered throughout the white matter of the brain (Fig. 1). The smallest of these were pinhead sized and consisted of well-defined grayish-pink plaques. The larger ones, which measured up to 5 cm. in diameter, had irregular borders and a peculiar gelatinous, yellowish, granular appearance. When the fluid oozed away after cutting, the tissue collapsed. In some of these lesions, cystic degeneration had occurred.

The frontal lobes and internal capsules contained only tiny foci, and none were seen in the temporal lobes. A large lesion occupied the right parietal lobe, extending from the cortex to the posterior horn of the lateral ventricle, and a slightly smaller one, which was partly collapsed, occupied the left occipital white matter. The entire white matter of the cerebellar hemispheres was degenerated; this extended through the middle cerebellar peduncles into the pons. The medulla and spinal cord were normal.

The lesions showed no predilection for any particular zone of the white matter, such as the subcortical regions, which had been reported in previous cases,[1] but rather were scattered haphazardly throughout. The arcuate fibers were not spared, and in certain areas, particularly the cerebellum, the deeper layers and occasionally even the whole thickness of the cortex was involved.

Microscopically, the lesions showed an extensive loss of myelin sheaths (Fig. 2) with relative preservation of the axis cylinders (Fig. 3). In the center of the larger foci, the axis cylinders also were destroyed. Some of the broken-down myelin was found in scavenger cells, which packed the areas (Fig. 2) and which in fat stains were shown to be swollen with sudanophilic droplets. The majority of these cells had the ordinary size of small macrophages, but a few were about 4 to 5 times as large, measuring 80 to 100 μ in diameter. The nuclei in these larger cells were occasionally multiple but were otherwise quite normal.

The most remarkable feature was the presence of monster astrocytes (Fig. 4). These were found mostly in the center of the lesion but occasionally also lay along the margins, being seen, for example, in the intact cere-

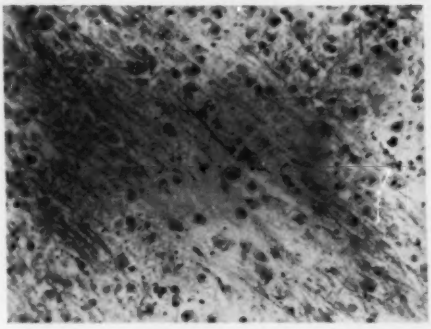

Fig. 2. Pons. The myelin sheaths end abruptly at the edge of a lesion. The scavenger cells contain dark granules which tinctorially are identical with myelin. Luxol fast blue, cresyl violet. × 150

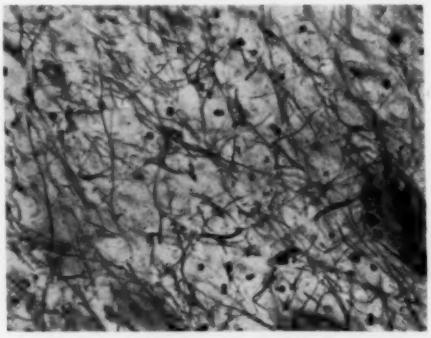

Fig. 3. Cerebellum. Axis cylinders in a lesion. Bodian stain. × 425

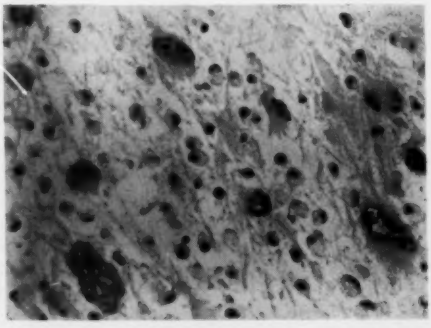

Fig. 4. Cerebellum. Monster astrocytes. Hematoxylin and eosin. × 375

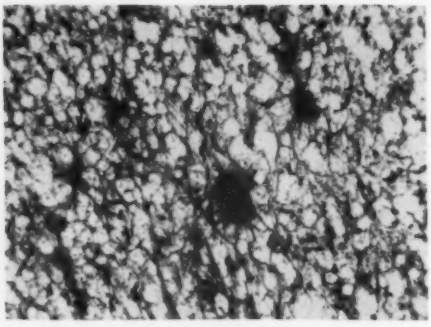

Fig. 5. Cerebellum. Monster astrocytes. Cajal's gold impregnation. × 125

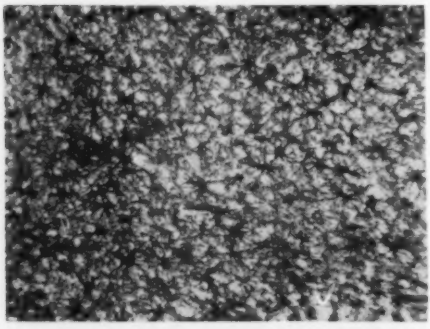

Fig. 6. Cerebellum. Reacting astrocytes. Same slide as Figure 5. Cajal's gold impregnation. × 125

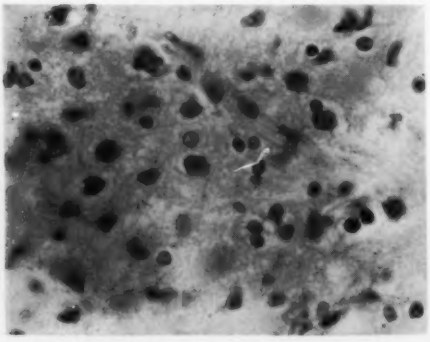

Fig. 7. Parietal lobe. Atypical oligodendroglial cells. Hematoxylin and eosin. × 425

bellar cortex as far out as the molecular layer. These cells measured, without processes, about 70 to 80 μ in diameter and were at least 5 to 6 times the size of normal reacting astrocytes. They had single or multiple nuclei, which frequently were bizarre in shape and often hyperchromatic. Cytoplasmic processes were seen easily in ordinary hematoxylin and eosin preparations but impregnated poorly with gold (Fig. 5) as compared to the normal reacting astrocytes (Fig. 6). A few of the monster cells were in mitosis.

The oligodendroglial cells in most regions were normal. In the right parietal lobe, however, at the edge of the large lesion, they showed the characteristic changes described by Astrøm[1]—swelling of the nucleus to 2 to 3 times normal size, with a change from the round to an angular shape and a homogenization of the nuclear chromatin (Fig. 7). The cytoplasm was scanty, pale, and slightly granular or clear.

No inclusion bodies could be seen in any type of cell.

The vessels were normal, but some were cuffed by lymphocytes. A few collections of lymphocytes lay in the ground substance, and, in the more recent foci, occasional small clusters of polyblastic microglial cells were encountered.

DISCUSSION

The pathologic features which set this disease apart from other demyelinations are the specific changes in the astrocytes and oligodendroglial cells. Although large astrocytes can be found with such conditions as Schilder's disease, they never assume such monstrous forms, nor are the oligodendroglial cells altered in the same manner. Moreover, the extension into the gray matter is quite uncharacteristic of ordinary diffuse sclerosis. The etiology is not known. Cytomegaly is seen in radiation damage and certain viral diseases. The effects of radiation or radiomimetic drugs have been considered,[2] but in only a few of the cases known can such treatment and onset of the disease be linked, while several patients had no therapy whatsoever. Viral inclusions, despite some suggestive findings, have not been adequately demonstrated histo-

logically, and no viral isolations have been attempted to date. The association with the lymphomas is striking but not invariable. It is tempting to try to relate the changes to some disorder of the reticuloendothelial system, a theory which would be applicable not only with the lymphomas but also with tuberculosis and sarcoidosis. Cavanagh[2] postulated on this basis a disorder of the immune mechanisms leading either to the formation of autoantibodies or facilitating the invasion by some, perhaps otherwise innocuous, virus or, because of the disordered reticuloendothelial metabolism, to a disturbance of the normal myelin metabolism. These, however, are speculations only, and the etiology of this illness is really as unknown as that of Schilder's disease, multiple sclerosis, and carcinomatous neuropathy.

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Changes in cerebral dynamics associated with seizures

Philip T. White, M.D., Phyllis Grant, M.D.,
Jack Mosier, M.D., and Alex Craig, M.D.

THE PRESENT INVESTIGATION has been undertaken to measure changes occurring in cerebral blood flow and cerebrospinal fluid dynamics during convulsions in human beings. Additional observations on the cardiovascular changes associated with seizures have been included. With succinylcholine and artificial respiration, the various changes in cardiovascular function, cerebrospinal fluid dynamics, and cerebral blood flow can be measured during the resting state and in the absence of physical activity. Some of the data pertaining to this technic have been previously published.[1]

Other authors have indicated that profound changes do occur in many vital functions in response to induced or spontaneous seizures. Early observations by Gibbs, Lennox, and Gibbs[2] indicated that seizures were not associated with cerebral vasoconstriction. Using a thermoelectric device, they noted an increase in blood flow through the internal jugular vein and a rise in blood pressure accompanying spontaneous seizures. They included a brief comment that there appeared to be no change in cerebrospinal fluid pressure before petit mal or grand mal seizures. Some of their measurements were impaired by the wide fluctuations in flow associated with muscular activity, struggling, and heavy breathing and by compression of veins of the neck with changes in posture. More direct observations by Penfield, Santha, and Cipriani[3] indicated that localized increases in blood flow were associated with partial or focal seizures and that with generalized seizures there was a more generalized increase in cerebral blood flow. Schmidt, Kety, and Pennes,[4] using the nitrous oxide cerebral blood flow measuring technic, have shown changes in blood flow during induced seizures in monkeys. Direct and indirect measurements in lower animals have also tended to show localized or generalized increases in blood flow associated with seizure activity.[5] In contrast, one report[6] attempted to show that vasoconstriction occurred in association with seizures in dogs. This conclusion was reached by estimating the size of vessels visualized angiographically.

It has been stated that the principal variable controlling cerebrospinal fluid pressure is the rate of intracranial blood flow.[7] Conditions otherwise being normal, an increase in arterial pressure and cardiac output results in an elevated cerebrospinal fluid pressure, presumably as a result of increased cerebral blood flow. It is felt that high venous pressure may help maintain elevated cerebrospinal fluid pressure but does not act as the primary agent for such elevation. Ryder and associates[8] have shown that changes in cerebral blood flow result in changes in cerebrospinal fluid pressure in the same direction. From changes in blood pressure, one may infer changes in cerebral blood flow, but the major controlling factor seems to be the cardiac output, for at times the cerebral blood flow may increase even though dissociated from arterial and venous pressures. The cerebral blood flow of monkeys has been shown to increase in response to increased cardiac output, resulting from convulsions induced by electroshock.[9]

A previous report by some of us has indicated that profound changes occur in blood pressure, heart rate, and electrocardiographic configuration in response to pentylenetetrazol-induced seizures.[1] Discrete electrical stimula-

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tion of the tip of the temporal lobe is associated with an increase in blood pressure, as indicated by Chapman, Livingston, and Poppen.[10] Several investigators have indicated that stimulation in areas of brain other than the bulbar cardiovascular centers can produce changes in electrocardiographic configuration, heart rate, and blood pressure, particularly when local seizure activity or after-discharge occurs.[11] Areas such as the motor and orbital frontal regions, hippocampus, fornix, and amygdala are said to influence these in some species and with certain parameters of stimulation. Richardson and associates[12] and Colville and associates,[13] in a large series of investigations of responses to transcranial electrical stimulation, have concluded that the profound cardiovascular changes are the results of generalized peripheral discharge of both branches of the autonomic nervous system, with the adrenergic influences predominating during the major part of the seizure. They noted that transection of the spinal cord or the use of ganglionic blocking agents prevented the rise in systolic and diastolic pressures. After adrenalectomy the systolic blood pressure failed to rise as dramatically in response to transcranial stimulation. The diastolic pressures were less influenced by the adrenalectomy. Thus, peripheral vasoconstriction, resulting from peripheral autonomic influences, and increased cardiac contraction and output, the effect of adrenal substances are factors in the response to transcranial electrical stimulation.

It is a well known clinical fact that certain types of spontaneous epileptic attacks are accompanied by a variety of autonomic changes. From these observations, the clinical term diencephalic epilepsy has been derived.

METHOD

For this study, epileptic patients with a variety of seizures were used. No attempt was made to select certain seizure types. Some of the patients had obvious neurologic signs, but there was no indication that any had a lesion that would influence cerebral blood flow measurements or spinal fluid dynamics directly.

Needles or polyethylene cannulas were inserted into the appropriate arteries and veins and the lumbar subarachnoid space after local anesthesia. Succinylcholine was administered by continuous intravenous drip, at a rate sufficient to completely abolish all muscle activity. A pneumatic tourniquet was placed around one ankle to prevent the effect of succinylcholine in that foot. This permitted us to observe some physical signs of seizure activity which could be correlated with the electrographic changes. Artificial respiration was maintained by an anesthesiologist using a bellows type of hand resuscitator or a hand operated positive pressure valve and mask. The latter was also used to administer nitrous oxide. The cerebral electrical activity was continuously monitored on an 8 or 16 channel Grass electroencephalograph. These instruments or a Grass polygraph were also used for continuous recordings of the electrocardiogram and the electromyogram from the isolated foot. Blood pressures were recorded intermittently with the use of a sphygmomanometer or continuously from one femoral artery using a Statham gauge and the polygraph. With the patient prone or in the lateral decubitus position, the spinal fluid pressures were measured continuously by a water manometer or a Statham gauge.

After it was determined that the various measurements were being recorded satisfactorily and the patient was in a relatively stable state, pentylenetetrazol was introduced intravenously until a seizure was induced. On some occasions, spontaneous seizures occurred, but, when pentylenetetrazol was used, it was given at the rate of 50 mg. every thirty seconds to 1,000 mg. and then if necessary an additional 100 mg. was given every thirty seconds. On some occasions, before injection of pentylenetetrazol, levarterenol was administered intravenously by continuous drip until the systolic blood pressure reached 200 mm. Hg. After the effect of this drug was dissipated, pentylenetetrazol was administered as described above. In 4 patients, procaine was introduced intrathecally, resulting in high cervical spinal anesthesia before the use of pentylenetetrazol. In addition to the other measurements, attempts were made to determine cerebral blood flow in 9 patients. The technic used was that described by Kety.[14] The determinations were carried out [1] during a resting state, [2] during the administration of succinylcholine alone, and [3] be-

ginning with onset of a seizure as indicated in the electroencephalogram and/or isolated foot.

A total of 49 adult patients, of whom 25 were female and 24 male, volunteered for the procedure; 56 investigations were undertaken, but for various reasons only 50 were considered technically adequate.

RESULTS

In 21 patients, the measurements of most of the changes during an induced nonfocal generalized convulsion were considered technically adequate. It was concluded that a generalized seizure was occurring when a combination of changes in the isolated foot and certain electrographic patterns were related. Electrographically, we would note a rapid build-up or an abrupt onset of high-amplitude, continuously intermixed fast, slow, and spike activity during which time the isolated foot would be tonically plantar flexed. This phase would merge into alternating spikes and slow waves accompanied by clonic movements of the foot. When the seizures subsided, there was abrupt flattening of electrical activity associated with or preceded by cessation of movements in the isolated limb. On some occasions, the seizure was preceded electrographically by an initial brief period of flattening or by an increase in paroxysms of high-amplitude bilaterally synchronous slow activity. The amounts of pentylenetetrazol necessary to induce these seizures varied from 100 to 1,600 mg., the average being 775 mg. The seizures varied in duration from thirty-five seconds to six minutes, the average being two and three-fourths minutes. All of the seizures were self-limited.

In all 21 cases, the resting blood pressures were within normal range. With onset of the seizure, blood pressure rose rapidly. The mean rise of the systolic pressure was 85 mm. Hg and of the diastolic pressure, 42 mm. Hg. The greatest change in systolic pressure was a rise of 170 mm. above the resting level and the least, a rise of 25 mm. Changes in diastolic pressure ranged from a high of 100 mm. Hg above the resting level to a low of 10 mm.

All but 4 of the 21 patients had normal heart rates before the seizure, the mean rate being 83. In all 21, with onset of a seizure, there was a marked acceleration of the heart rate above the resting level. The mean rise above resting was 83 per minute, ranging from 24 to 125. Peak rates of 180 or more were frequent. In 1 instance, the resting rate was 60 and rose to 185 during the seizure. The fastest rate encountered was 195, the resting rate having been 80.

Momentarily after these changes in heart rate and blood pressure occurred, the cerebrospinal fluid pressure rose quickly. In 4 of the 21 patients, the resting spinal fluid pressure was above 200 mm. H_2O. The others were below the usually accepted upper limits of normal, the average resting pressure being 177 mm. H_2O. The mean rise in pressure above the resting level was 549 mm. H_2O, the least being 270 and the most 800. On 1 occasion, the peak pressure during a seizure was 1,000 mm. H_2O, the upper limit of the measuring apparatus.

The temporal relationship of these changes is of interest, although these are approximate ones since the measurements of the various changes were often intermittent rather than continuous. The polygraphic records with continuous recordings support the figures found with intermittent measurements. In all but 3 cases, heart rate and blood pressure elevations were detected before elevation of the cerebrospinal fluid pressure. In these instances, the rise in blood pressure appeared to lag behind because of infrequent measurements of the blood pressure at this critical moment. The initial changes as well as the peak values of these various responses maintained this temporal relationship. On the basis of average time of occurrence after onset of a seizure, the fastest heart rate was reached in fifty-two seconds, the peak blood pressure in sixty-six seconds, and highest cerebrospinal fluid pressure in seventy-seven seconds. Figures 1 and 2 show changes and their time relationships.

Serendipitous spontaneous seizures of a generalized type were recorded on 3 occasions. The changes and time relationships were of the same order as those occurring with the induced seizures. On 1 occasion, with a seizure lasting sixty-five seconds, the heart rate accelerated from 85 to 196 in twenty seconds, the blood pressure rose from 125/65 to 210/120 in thirty seconds, and the cerebrospinal fluid pressure from 160 mm. H_2O to 550 mm.

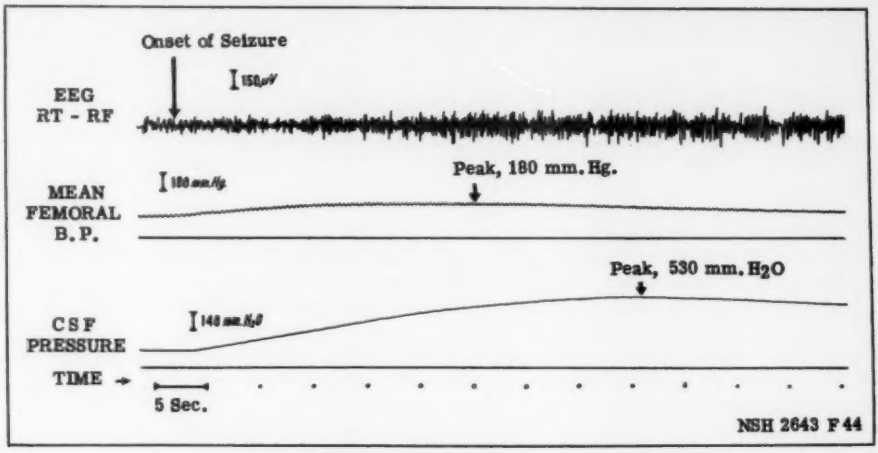

Fig. 1. Changes in blood pressure and cerebrospinal fluid dynamics during a seizure induced with 400 mg. of pentylenetetrazol. Tracing is segment of polygraph recording obtained during seizure. Increase in cardiac rate could be more clearly seen in electrocardiographic tracing taken separately.

in thirty seconds. The other 2 spontaneous seizures showed similar but less profound changes due to their brevity; 1 lasted nine seconds and the other only seven, so responses were barely initiated when the seizure ended.

On several occasions, marked focal changes were recorded electrographically, either spontaneously or with pentylenetetrazol. It was considered that these represented partial or focal seizures, as the pattern consisted of increasingly frequent recurrence of localized spike activity of rapidly increasing amplitude, simulating a localized after-discharge. On some occasions, this would spread to other areas and a generalized convulsion would ensue. Regardless of the area of appearance of

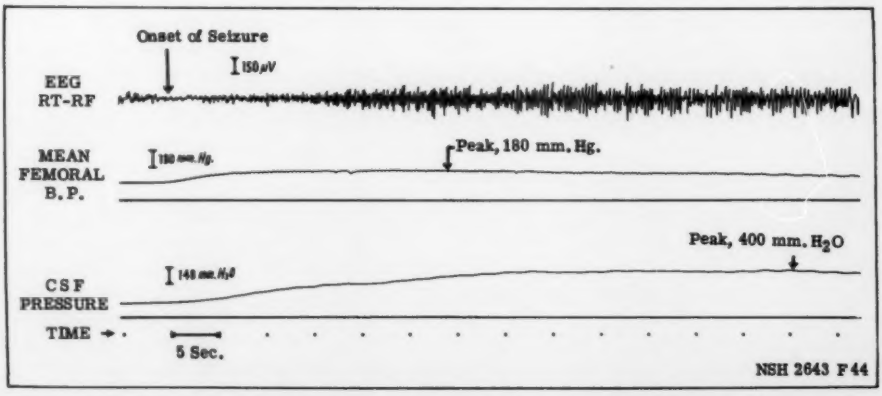

Fig. 2. Changes similar to those seen in Figure 1 but here associated with seizure induced with 1,100 mg. of pentylenetetrazol, indicating changes are not proportional to amount of drug used.

this focal electrographic pattern, little or no change occurred in the cerebrospinal fluid pressure, blood pressure, or heart rate. If, however, the activity became generalized, minor alterations often heralded the onset of a generalized seizure shortly before it could be detected electrographically. These minor variations are seen in Figure 3C and D. In 2 patients known to have petit mal seizures clinically, a series of generalized spike-wave patterns preceded the generalized seizure. In 1, there was no appreciable alteration in the measurements until the major convulsive pattern arose in the electroencephalogram. In the other patient, what appeared to be a petit mal state continued for approximately five minutes before progressing into a generalized seizure. During that time, the resting heart rate rose erratically to 138 and, forty seconds after onset of the major seizure pattern, rose to 190. The resting blood pressure was 105/60. At the moment just preceding the generalized seizure pattern, it had risen erratically to 145/90, but, fifty-five seconds after onset of the major seizure, it reached 210/90. A similar change was noted in the cerebrospinal fluid pressure. From a resting value of 110 mm. H_2O, there was an irregular rise to 170 by the end of the minor phase, followed by a further rise to 750 after sixty-eight seconds of the major seizure.

In 4 patients, the responses to induced generalized seizures were recorded after the establishment of high spinal anesthesia. In all 4, the cerebrospinal fluid pressure rose as before but the changes were somewhat less profound. The increases ranged from 190 mm. H_2O to 440 mm., with an average rise of 285 mm. above the resting values. In contrast, little change was noted in the blood pressure. There was no difference in the mean diastolic pressure, but the mean systolic pressure during seizures was lower than during the resting state. The average rise in heart rate was 30. The time relationships of the changes in the heart rate and cerebrospinal fluid pressure were the same as those recorded in the absence of spinal anesthesia. In these 4 patients, the entire procedure was repeated without spinal anesthesia and the results were comparable to those observed for the previously described 21 patients.

An attempt was made to define the relationship between the changes in cerebrospinal fluid pressure and elevated blood pressure. In 13 patients, under the same conditions in which seizures were induced, levarterenol was given intravenously until the systolic blood pressure rose to approximately 200 mm. Hg. After the pressure had returned to a resting level, pentylenetetrazol was given as described previously and a seizure induced. In these 13 patients, the average resting blood pressure was 122/74. The rise in blood pressure produced by levarterenol was comparable to that attained during pentylenetetrazol-induced seizures. The average rise of systolic pressure above the resting level was 85 mm. Hg during seizure activity and 87 mm. Hg during administration of levarterenol. The rise in diastolic pressure above the resting level averaged 42 during the induced seizure and 37 during administration of levarterenol. In contrast, the rise in cerebrospinal fluid pressure was never as prompt nor as great in degree with the administration of levarterenol. The average resting cerebrospinal fluid pressure was 178 mm. H_2O. The rise above the resting values with levarterenol ranged from no rise to a high of 300 mm., the average being 135. This was considerably less than the rise occurring with induced seizures, which was 549 mm. Figure 3 represents the responses to levarterenol contrasted with those during a seizure.

In 9 patients, attempts were made to measure the changes in cerebral blood flow associated with induced seizures. Because of the need to give the gas mixture artificially, the prolonged nature of the procedure, the brevity of some seizures, and the occurrence of seizures at undesired times, additional technical difficulties were encountered. As a consequence, the absolute value of blood flow in each case may not be accurate. In 4 instances, the procedure was incomplete. However, in 5 of the 9 patients, there seemed to be a pattern, the resting blood flow values ranging from 39.8 to 78, with a mean value of 56.3 cc. of blood per 100 gm. of brain tissue per minute. During paralysis with succinylcholine, these respective values were 25.9, 50.9, and 40. During induced seizure activity, the cerebral blood flow ranged from 58.9 to 135.4, with a mean value of 92.5 cc.

of blood per 100 gm. of brain per minute, indicating an increase in cerebral blood flow during seizures.

Major or minor cardiac irregularities were noted in the electrocardiograms of 26 patients. These most frequently occurred as the seizure was subsiding and the blood pressure falling toward normal. Some occurred at the height of the blood pressure rise or as the pressure began rising. These irregularities varied and consisted of premature auricular or ventricular rhythms, elevated or depressed ST segments and T waves, conduction blocks, ventricular tachycardia, and prolonged bradycardia with coupling. In 1 patient, there was evidence of severe myocardial ischemia. The table is a summary of the various changes.

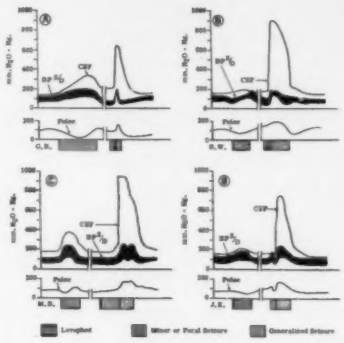

Fig. 3. Graphs show changes occurring with levarterenol as compared to those during induced seizure. Time base has been shortened, with proper proportions maintained. C and D indicate some of the minor changes occurring just before seizure onset.

DISCUSSION

The use of the technic we have described demands certain precautions. A competent anesthesiologist is required to assure a patent airway and adequate respirations. One must recognize that the patients are conscious and often apprehensive until the seizure occurs and that their mental and physical comfort need attention. It is possible to communicate with the patient before onset of the seizure because he can respond in a positive or negative fashion by changes in posture of the isolated foot. He can thus be kept reasonably comfortable and assured. After the seizure, there is usually amnesia for the entire event. Some memory of the preliminary procedure ultimately returns, but there is rarely any recall of undue pain or discomfort.

Even though large quantities of pentylenetetrazol were occasionally used, no apparent complications arose therefrom. At no time was status epilepticus precipitated. In some of our earlier preliminary studies, oxygen instead of compressed air was used for artificial breathing. Occasionally, a repetitive series of seizures would occur under these circumstances, requiring the use of barbiturates to terminate. Meyer and Portnoy[15] suggested that the postepileptic condition of neuronal exhaustion was related to a low cortical oxygen tension and that spike activity resumed when this tension rose. By using 100% oxygen, we may have forestalled neuronal exhaustion.

Under the circumstances surrounding these particular studies, the determination of cere-

CHANGES ABOVE OR BELOW THE RESTING VALUES IN HEART RATE, BLOOD PRESSURE, AND CEREBROSPINAL FLUID PRESSURE

	Pulse (rate per minute)			*Blood pressure (mm. Hg)* S		SS		L		*Cerebrospinal fluid pressure (mm. H_2O)*			*Cerebral blood flow (cc. per 100) gm. of brain per minute)*		
	S*	SS†	L‡	Sys.§	Dia.¶	Sys.	Dia.	Sys.	Dia.	S	SS	L	R**	SC††	S
High	125	43	+30	170	100	+10	+10	120	70	800	440	300	78.0	50.9	135.4
Low	24	13	−106	25	10	−20	−5	55	15	270	190	0	39.8	25.9	58.9
Mean	83	30	−7	85	42	−8	0	87	37	549	285	135	56.3	40.0	92.5

*Induced seizures
†Seizures during spinal anesthesia
‡Levarterenol
§Systolic
¶Diastolic
**Resting state
††Paralysis with succinylcholine

bral blood flow becomes a more complex procedure. One must be frugal with the amounts of heparin used. The introduction of a needle into the internal jugular bulb may not be as innocuous as described.[16] There is obviously some variation in the anatomy of that region. On 2 occasions, cerebrospinal fluid was obtained, and the carotid artery was punctured on other occasions. It is conceivable that more vital structures could be reached by the exploring needle. Our present inability to measure instantaneous changes in blood flow is a serious limiting factor. It may well be that the cerebral blood flow varies considerably during the different phases of a seizure. Our results provide only an average value at a time when many fluctuations may be occurring.

CONCLUSIONS

The use of succinylcholine before induction of seizures permits more accurate observations of many of the associated physiologic changes. As we have pointed out previously, the electroencephalographic changes are no longer beclouded by muscle artifact. Furthermore, the alterations in functions are the direct or indirect result of the demands of increased neuronal activity. There is no need to subtract responses possibly due to physical activity. The procedure is safe for human beings.

The data derived from these studies, as well as those of others, indicate that a generalized seizure results in alterations in many vital functions. The exact mechanisms responsible for these changes cannot be precisely identified. The depth studies on lower animals suggest that there may be controlling centers which, when activated, produce alterations in heart rate, electrocardiographic configuration, and blood pressure. It must be kept in mind that species differences do exist and the translation of results must be approached cautiously. Furthermore, it is germane to question whether localized seizure activity or after-discharge due to electrical stimulation is equivalent to a seizure and its more complex, integrated—even though pathologic—activity of multiple regions. We have shown that there are pronounced differences in the responses to petit mal, localized, and generalized seizures. We cannot be certain of the precise areas producing these focal and minor seizures, but the results do suggest that alterations occur because of integrated overactivity of several regions rather than of a single controlling center.

We are aware that an adequate oxygen tension is necessary for maintenance of seizure overactivity. It is reasonable to assume that, to maintain this level during a seizure, a greater cerebral blood flow is necessary and this results from the integrated activity of various regions and systems. Perhaps the areas responsible for autonomic changes may not be directly involved by the spread of seizure activity but become activated indirectly by this demand for increased blood supply in the brain regions occupied by the seizure. Thus, the bulbar-reticular-autonomic regions become activated. Certain regions, such as the hippocampus, may be more dependent upon a certain blood supply for continued overactivity and bulbar autonomic centers more sensitive to its demands. Stimulation in such regions could cause misleading site-specific responses.

We surmise that the physiologic changes associated with convulsions are the result of the integrated action of many regions, in this way assuring an adequate oxygen supply to those areas overwhelmed by the abnormal seizure activity and the increased cerebral metabolic rate. As the bulbar-reticular-autonomic centers are signaled, a chain of events begins. Peripheral autonomic activity increases. An associated intracranial vasodilation, increased localized arterial drainage, and a localized drop in blood pressure occur. These alterations, too, result in further autonomic changes, producing an increased rate and vigor of heart contraction with a subsequent increased cardiac output. This, plus the subsequent peripheral vasoconstriction and the intracranial vasodilation, results in increased cerebral blood flow. The elevated cerebrospinal fluid pressure reflects this increase of cerebral blood flow. Generalized vasoconstriction is a contributing factor, as shown by the lower cerebrospinal fluid pressure values during spinal anesthesia. A rise in blood pressure alone is not sufficient, as shown by the changes occurring with levarterenol. Figure 4 is a schematic representation of the interdependent factors responsible for the increase in cerebral blood flow and cerebrospinal fluid pressure. This theoretic chain of events is not initiated

by localized overactivity—as with petit mal or focal seizures—as least to the same degree.

Many of the electrocardiographic changes appear to be due to secondary changes in the heart and its conducting mechanisms rather than to impulses from specific brain centers. It should be noted that the vast majority of changes coincided with the end of seizure activity rather than its beginning or climax.

Perhaps a combination of the procedures described herein and depth electrodes would help to more clearly elucidate the mechanisms involved in producing these changes in blood flow, cerebrospinal fluid dynamics, and cardiovascular function. In the meantime, one must be cautious about assigning specific functions to single specific areas.

SUMMARY

An investigation of changes in heart rate, blood pressure, electrocardiographic configuration, cerebrospinal fluid pressure, and cerebral blood flow associated with induced generalized convulsions has been undertaken. With the use of succinylcholine and artificial respiration, these changes can be measured in human subjects and related to neuronal overactivity. The increased cerebrospinal fluid pressures reflect the increased cerebral blood flow. Changes during partial or focal seizures are less profound. The increased neuronal activity of a generalized convulsion requires greater blood flow. Marked cardiovascular changes occur to provide this greater blood flow.

We gratefully acknowledge the assistance of Mr. LaMoine Jackson and our other EEG and laboratory personnel.

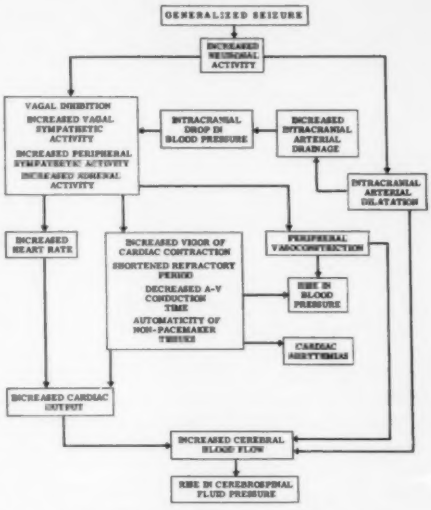

Fig. 4. Integrated changes resulting in increased cerebral blood flow and elevated cerebrospinal fluid pressure during generalized convulsion. Vagal inhibition implies a decrease in vagal parasympathetic activity.

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Motor function after spaced contralateral hemisections in the spinal cord

Arthur M. Lassek, Ph.D., M.D., and Patricia A. Anderson, B.S.

THOUGH THE SPINAL CORD forms a small portion of the central nervous system quantitatively, it carries on manifold and important functions involving structures in the major part of the body. As such, it offers an opportunity to investigate basic factors in restitution of voluntary motor function, a phenomenon which has been difficult to explain on neurologic grounds.

We have approached the problem by making lower hemisections between the phrenic center and the second thoracic spinal cord segment, following high cervical hemisections on the opposite side. This permits observations to be made on the immediate and long-range effects of the second hemisection on the opposite recovered side, as well as the remaining nerve pathways from higher centers.

MATERIAL AND METHODS

A left hemisection of the spinal cord was first performed in 7 Macaque mulatta monkeys, 6 at the level of the second cervical segment and 1 at the first. The animals weighed 6 to 10 lb. and were in good preoperative physical condition. The length of time allowed for motor restitution varied from seventy-two to five hundred thirty-two days, the average being two hundred seventeen. Throughout the investigation, each animal was observed in the cage, as well as given periodic neurologic examinations. Tone, resistance to passive movement, checking reactions, grasping and tendon reflexes, and ability to perform phasic movements were stressed.

A second operation, a right hemisection below the phrenic center, varying in level from C6 to T1, was then performed. Again the animals were examined and observed. Postoperative intervals varied from fifteen to ninety-three days, an average of forty-six; the time of sacrifice depended upon the physical condition of each monkey.

Immediately before sacrifice, the motor cortex in 3 animals was stimulated electrically, either unilaterally or bilaterally. A voltage range of 1 to 15, frequency 60, was used in each case.

After removal at autopsy, the spinal cord in each instance was studied grossly and histologically to determine the exact extent of the hemisections. After fixation in 20% formalin and Protargol fixatives, sections were stained by Weil's myelin sheath, Kluver's luxol-blue, Davenport's silver, and Protargol methods.

RESULTS

After initial left upper cervical hemisection, the 7 animals used in the experiments showed an immediate flaccid paralysis of the ipsilateral upper and lower extremities. On examination, these limbs dropped from an elevated position as a dead weight. No grasping reflex could be obtained. Little or no tone or resistance at the joints was found, and no phasic movements were possible. The right extremities appeared normal in all respects.

Restitution of motor function after complete paralysis in the limbs was evidenced by the following: return of tone to a normal or near normal level, a checking reaction when the extremity was dropped, supportive adjustments, and definite phasic movements. Little or no atrophy of muscles was noticeable on the affected side. Although a preference was usually shown for picking up food with the

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normal hand, at times this was done with the affected fingers. This degree of recovery occurred at rates which varied with each animal, the shortest length of time being about forty days and the longest seventeen months.

When contralateral right hemisection at the lower cervical or high thoracic level was made, severe and lasting motor paralysis involving both sides occurred below the level of this lesion. For example, when an incision was made at C6, the voluntary motor centers of both sides were affected distally to the lowermost part of the spinal cord. The restored function was completely and permanently lost. Each animal presented the picture of paraplegia, with partial involvement of the left upper extremity.

So severe was the bilateral motor deficit in the 7 monkeys that none was able to climb up to and sit on a crossbar, though they made attempts to do so; 1 could neither assume a sitting position nor climb and pressure sores at the hip and knee joints developed in 2.

The type of paraplegia was initially flaccid due to the hypotonic condition of the muscles. Reflex responses, using the patellar as an example, were highly variable, making it difficult to formulate any general conclusions. After the passage of several days, the response was generally characterized by having a decreased threshold, an increase in amplitude, diminution in force, and a loose, pendulous character. Partial exaggerated resistance to passive extension at the hip, knee, and ankle joints, which could be overcome only with difficulty, was observed in 4 cases; this was a late development. At no time was retention of the urine in the bladder noted, though both halves of the spinal cord were hemisected relatively high up, simulating a transection.

In 3 monkeys with the spaced contralateral hemisections, the motor cortex was stimulated electrically before sacrifice. Excitation of the right area 4 in 1 produced no movement of either left extremity. In another animal, stimulation of the left motor cortex induced a response in the normal right upper extremity but not the right lower. Both motor cortices were stimulated in a third animal, resulting in no movement of any limb except the right arm.

The stained sections through the level of the 14 hemisections made in the spinal cord of the 7 monkeys were studied serially. In all instances, the operative incision passed along the posteromedian sulcus, through or near the central canal of the gray commissure, along the anteromedian fissure; 5 were accurately placed. In 9 instances, the cut missed the exact midline. In 4, the anterior funiculus was spared slightly on the same side as the hemisection. Twice, the anterior funiculus of the side opposite to the hemisection was narrowly involved. Once, the posterior funiculus of the contralateral half was barely incised, and, twice, both the homolateral posterior and anterior funiculi escaped the lesion near the midline. We believe that these minor deviations did not measurably alter the symptoms.

DISCUSSION

The effect of ipsilateral hemisections at different levels has been studied in several species: by Rizzolo[1] in the cat; by Rossolymo[2] in the guinea pig; by Homen,[3] Kusmin,[4] Osawa,[5] and Weiss[6] in the dog; and by Mettler,[7,8] Turner,[9] and Mott[10] in the monkey. In respect to restitution of motor function after initial paralysis, all report complete or nearly complete physiologic recovery, the time factor varying but in general being remarkably short.

Mettler,[8] the most recent investigator in the above group, made high unilateral hemisections in the spinal cord in 3 monkeys, as a part of his general studies on the effects of large subtotal lesions, and noted quick return of motor function after paralysis. The step-by-step restitution of the affected upper limb in one protocol is as follows: useful in climbing, one week; defense and bimanual feeding, one month; monomanual feeding, six weeks; opposition of thumb, two months; and ability to use as well as the normal upper hand, two and one-half months. Whereas our animals showed essentially the same series of events, some exhibited more latent recovery, indicating variability in this respect.

The above results with unilateral hemisected spinal cord of rodents, carnivores, and monkeys indicate that there is a large safety factor, under experimental and laboratory conditions, as far as voluntary motor physiology is concerned.

After our experimental program was under way, we discovered 2 papers published about seventy years ago, reporting contralateral hemisections made in the spinal cord in 2 monkeys.[9,10]

Turner[9] performed a right hemisection at segment T9 in 1 experiment. Sixty-eight days postoperatively, after motor restitution had occurred, a second was made at T6 on the left side. Complete paralysis of both lower extremities occurred immediately, which persisted until the animal was sacrificed, forty-three days after the second operation and one hundred thirteen days after the first. Both lower limbs became contracted, rigid, and atrophied.

Mott[10] first made a right hemisection between T3 and 4 in the monkey. This also resulted in total paralysis of the muscles of the right leg. Thirty days later, the animal could flex the hip and knee and support itself with its right foot on the bars of the cage but was unable to grasp with it. On the thirty-second day, a lower left hemisection between T9 and 10 was performed. Twenty-four hours later, the monkey exhibited complete paraplegia. The animal died a week after this operation, and no further report of its motor condition was given.

Though our contralateral hemisections were made at different spinal cord levels than those of Mott[10] and Turner,[9] our findings harmonize in that the second lesion invariably causes a total and lasting paralysis in the opposite, restituted limb.

Our experiments were designed so that the upper right part of the spinal cord was left intact. Though this remaining portion was able to maintain normal function on the same and opposite recovered sides above the level of the lower right hemisection, it could not exert any nervous influence on the left lower extremity, leading toward secondary motor recovery. This finding eliminates the theoretic possibility that pyramidal tract or other extrapyramidal motor fibers decussate at cervical levels in sufficient numbers to be effective in this respect.

Though we did not give major attention to the reaction of the urinary bladder to the double contralateral hemisections, which were spaced regionally and chronologically, it may be of interest to mention that we did not observe retention of urine, which commonly occurs in man after severe lesions or transections of the spinal cord. Admittedly, the innervation of the bladder is a complex function, and we do not have an explanation to offer for this finding.

If one considers the two lateral halves of the spinal cord separately from the standpoint of descending nervous impulses entering from higher centers, which act on voluntary motor muscles, it appears that one-half is largely expendable in rodents, carnivores, and monkeys. The ability to perform postural and phasic movements returns after high cervical unilateral hemisections to such degree that the animals adjust quite normally to their laboratory environment. Eliminating the descending efferent impulses of the contralateral half of the cord by means of a second, lower hemisection produces a devastating effect below the level of the lesion, involving the muscles of both sides, from which no return of function can occur.

The key to understanding restitution of motor function may lie in understanding how descending nerve impulses in the spinal cord of one side, originating from higher centers, act on the anterior horn cells below in such a way as to affect those on the opposite side, leading to recovery from paralysis, when it exists. Believing that restitution may occur on a segment-to-segment basis, we have experiments under way to test the effect of midline cord incisions in the cervical enlargement in monkeys which have recovered voluntary motor function after high cervical unilateral hemisection.

CONCLUSIONS

1. A large safety factor exists following experimental injury to the spinal cord in the monkey.

2. From a state of complete paralysis after left hemisections at C1 or 2, voluntary motor function returns to near normal or normal levels. The speed with which recovery occurs varies.

3. When a contralateral hemisection is made below the phrenic center (lower cervical or upper thoracic), complete and lasting paralysis occurs in the right and in the left

(recovered) muscles below the level of the lesion.

4. Under the standards used in the experiments, retention of urine in the bladder was not observed.

The authors wish to acknowledge the technical assistance of Salvatore Lunetta.

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Cautions: In patients receiving Urevert during craniotomy, there is a consistent pattern of blood pressure increase averaging 26 mm. Hg. above stabilized blood pressure, which occurs even in cases with significant blood loss. When adequate blood replacement is not initiated, this rise is later followed by a decrease, to an average of 20 mm. Hg. below stabilized blood pressure. Thus in craniotomies, when there is excessive blood loss within a short period of time, blood replacement should be adequate, and simultaneous with Urevert administration.

Contraindications:

1. Severe renal or hepatic damage.
2. Active intracranial bleeding.
3. Marked dehydration.

Caution: Lower extremity infusion in older patients is recommended.

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APRIL 1961

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Academy Poised for Annual Meeting

AAN members, their families, and guests are ready to convene for the Thirteenth Annual Meeting of the American Academy of Neurology to be held in Detroit's Sheraton-Cadillac Hotel April 24 through 26, 1961. Activities will begin with A. B. Baker's special review courses, which will be given April 24 through 26. The Scientific Programs start on April 27 and last through April 29. The Registration Chairman is Christian Herrmann, Jr. The AAN Women's Auxiliary has aided in the planning of a lively program of social activities. On Wednesday, April 26, AAN members and their wives are invited to the Early Bird cocktail party to be held in the Book Casino. On Friday, April 28, the Auxiliary has programmed a luncheon and a tour to Greenfield Village. Later, cocktails will be served for Academy members and their wives in the casino. That night, the annual banquet followed by dancing until midnight will be held in the grand ballroom. The Auxiliary points to the sight-seeing opportunities in Detroit: huge factories with their fine examples of automation, art exhibits of international renown, novel public buildings, collections of historical interest, Greenfield Village, the Henry Ford Museum, and many other attractions. A short distance from the Sheraton-Cadillac Hotel are the Detroit Institute of Arts, the Detroit Historical Museum, and Wayne University.

Elevation of Active Members to Fellows

Richard L. Masland, Chairman, AAN Subcommittee on Membership, requests that all AAN Fellows scan the list of active members and propose the names of those whom they consider deserving of elevation to fellowship. The proposal should be accompanied by biographical sketches of the candidates. According to the AAN constitution, Fellows of the Academy are defined as "members elected from among persons (a) who have been certified by the American Board of Psychiatry and Neurology in neurology and (b) whose chief interest is directed toward the field of organic neurology or whose clinical practice is limited chiefly to neurology." In general, this title has been reserved for neurologists in full-time academic work with senior appointments and/or significant research contributions. All communications should be addressed to the AAN Executive Offices, 4307 East 50th Street, Minneapolis 17, Minn.

Baldwin Appointed NINDB Clinical Director

Maitland Baldwin, Chief since 1953 of the Surgical Neurology Branch of the National Institute of Neurological Diseases and Blindness, has been appointed NINDB Clinical Director. In his additional post as Clinical Director, he succeeds G. Milton Shy, who has been appointed to the newly created position of Associate Director in Charge of Intramural Research at the Institute.

NINDB Film Wins International Award

A new NINDB film for professional use entitled "The Neurological Examination of the Newborn," prepared under technical direction of Richmond Paine, was awarded a Diploma by the Fourteenth General Assembly of the World Medical Association in recognition of its "Excellent standing among the medico scientific teaching and postgraduate training films of the world." Prints of the film may be purchased or rented from Churchill-Wexler Film Productions, 801 N. Seward Street, Los Angeles 8, Calif. A small number of copies are available on loan through the National Institute of Neurological Diseases and Blindness for professional audience showings.

Mount Sinai Symposium on Oculomotor System

Morris B. Bender has announced the holding of a symposium on the oculomotor system in the Blumenthal Auditorium of the Mount Sinai Hospital in New York City, April 14 and 15, 1961. Participating in the symposium will be many outstanding neurologists and neurologic scientists in this field from here and abroad. Among the distinguished visitors will be R. Warwick (London); J. Szentagophai (Budapest); H. H. Kornhuber (Freiburg); P. A. Merton (Cambridge, England); R. M. Pritchard (Montreal); and C. S. Hallpike (London). The chairmen of the symposium are Morris B. Bender, R. B. Livingston (Bethesda), and James L. O'Leary (St. Louis). The symposium is supported by a grant from the National Institute of Neurological Diseases and Blindness.

Neurovegetative Symposium To Be Held in Turin

The International Society of Neurovegetative Research will hold its eleventh symposium in Turin, Italy, June 11 through 14, 1961. The principal topics to be considered and discussed are obesity and the central mechanisms of the nervous functions of the skin. The symposium has been organized by Professors Lunedei (Florence), Midana and Ormea (Turin), and A. Sturm (Wuppertal-Barmen). The Secretary-General of the Symposium is Professor Ormea, Dermatological Clinic of the University, Via Cherasco, 23, Turin, Italy.

Chartered Flight to Europe and Return Charles M. Poser announces that he has made arrangements with British Overseas Airways Corporation for chartered transporation of AAN members who wish to attend the neurologic congresses in Europe. The flight departs from New York to Paris August 27, 1961, on a DC-7-C, with a return from Paris to New York September 29, 1961, on a Brittania 102 (jet prop). These planes have a seating capacity of 86 passengers. The chartered flight has been planned for those who wish to attend the EEG course in Marseille August 28 to September 2; the Fourth International Congress of Neuropathology in Munich September 4 to 7; the Seventh International Neurological Congress in Rome September 10 to 15; and the Fifth International Congress of EEG and Clinical Neurophysiology September 7 to 13. The fare per person (round trip only) is $280 payable in full before May 1, 1961. Money will not be refunded after May 15, 1961. Reservation requests and checks should be sent to Dr. Charles M. Poser, University of Kansas Medical Center, Kansas City 12, Kansas. The American Academy of Neurology assumes no responsibility for this charter, the contract being signed by Dr. Poser as the representative of persons making reservations.

Windle Returns from Puerto Rico William F. Windle, Assistant NINDB Director, recently returned from four months of intensive work at the NINDB Laboratory of Perinatal Physiology at the University of Puerto Rico Medical School. The studies in Puerto Rico are focused principally on the effects of adverse factors imposed on Rhesus monkeys during gestation, birth, and early postnatal life. It is operated in conjuction with NINDB's free-ranging colony of Rhesus monkeys on Cayo Santiago. Recently, a Scientific Advisory Committee for the Puerto Rico project was appointed by NIH Director, James A. Shannon. The committee is chaired by Louis B. Flexner and includes Leonard Carmichael, Secretary of the Smithsonian Institute; Leslie B. Arey (Chicago); Allan C. Barnes (Baltimore); Heinrich Kluver (Chicago); and Leon Schmidt (Cincinnati).

Advanced Course in Electroencephalography An advanced course for experienced electroencephalographers and technicians will be given at the University of Aix-Marseille August 28 through September 2, 1961. The course will be conducted under the auspices of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology and the Council for International Organizations of Medical Sciences (CIOMS). Purpose of the course is to give an intense teacher-training program in EEG and to provide a forum for the exchange of views and ideas. The course will center on problems of recording and interpretation as they relate to the

electroencephalographer in his work. It will present fundamental principles of recording and interpretation of the EEG; the physiopathologic significance of different phenomena characteristically observed in the EEG; and guidelines of normality in the EEG. Opening addresses will be given by Professor F. Bremer (Brussels), Herbert Jasper (Montreal), and Dr. W. Grey Walter (Bristol), who will be joined by Professor G. Morin, Dean of the University, and Professor Henri Gastaut. The faculty will consist of distinguished international authorities. Facilities will be available for simultaneous interpretations of English to French and French to English. Registration fees for the course are $25 for electroencephalographers and $10 for technicians. All inquiries and communications should be addressed to the Secretary, Dr. O. Magnus, St. Ursula Clinic, Wassenaar, Holland.

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1. Schwab, R. S. and England, A. C.: *J. Chron. Dis. 8*:488 (Oct.) 1958.
2. Kruse, Walter K.: *Dis. Nerv. System 21*:80 (Feb.) 1960.
3. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
4. Doshay, L. J., *et al.*: *J.A.M.A. 160*:348 (Feb. 4) 1956.

Full dosage information, available on request, should be consulted before initiating therapy.

6P12

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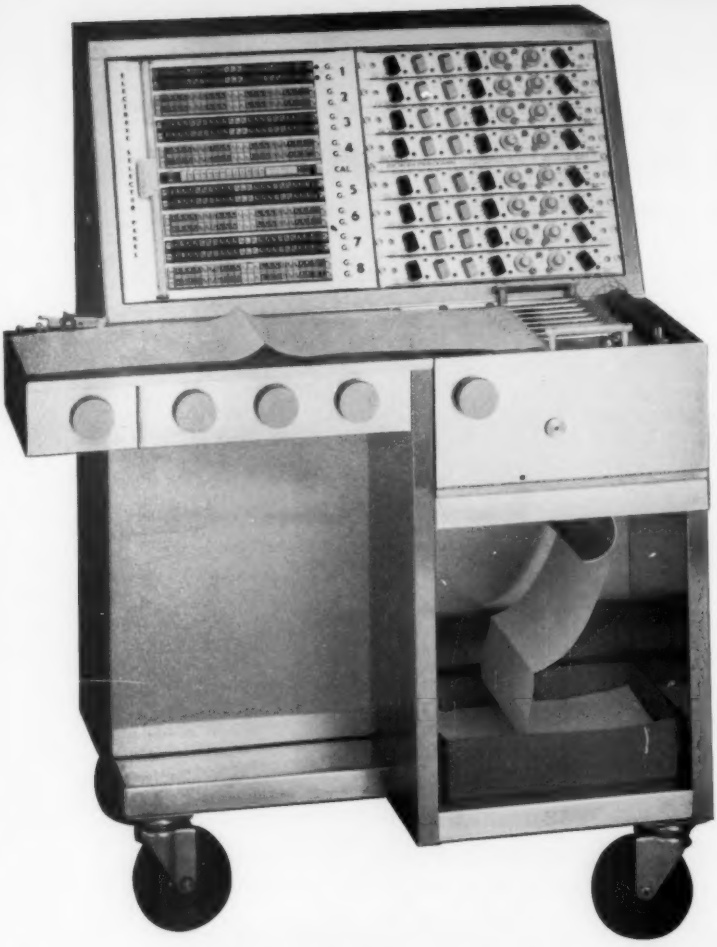

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BASIC ELECTROENCEPHALOGRAPHY—April 24, 1961. Dr. Fernando Torres. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROCHEMISTRY—April 24, 1961. Dr. Maynard M. Cohen and Dr. Donald B. Tower. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

METABOLIC DISORDERS OF THE NERVOUS SYSTEM—April 24, 1961. Dr. Gilbert H. Glaser. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

ADVANCED CHILD NEUROLOGY—April 25, 1961. Dr. Michael E. Blaw and Dr. Paul M. Ellwood, Jr. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

THE ELECTRON MICROSCOPE AND THE NERVOUS SYSTEM—April 25, 1961. Dr. Augustus S. Rose. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEWER CONCEPTS OF HUMAN CEREBRAL ORGANIZATION—April 25, 1961. Dr. John S. Meyer. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEURORADIOLOGY—April 25, 1961. Dr. A. L. Sahs. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

ABNORMAL STATES IN NEUROPHYSIOLOGY—April 26, 1961. Dr. James L. O'Leary. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

ADVANCED ELECTROENCEPHALOGRAPHY—April 26, 1961. Dr. Frank Morrell. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

MEDICOLEGAL ASPECTS OF NEUROLOGY—April 26, 1961. Dr. Royal C. Gray. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

In addition a special review course in Common Neurologic Diseases is offered to General Practitioners on Wednesday, April 26, 1961. The registration fee is ten dollars. Credit will be given by the American Academy of General Practice. This course is not available to members of the American Academy of Neurology. Dr. Benjamin Boshes is Course Chairman.

ENROLLMENT FOR ALL COURSES IS LIMITED

Priority will be determined by date of application.
No application will be accepted after April 14, 1961.

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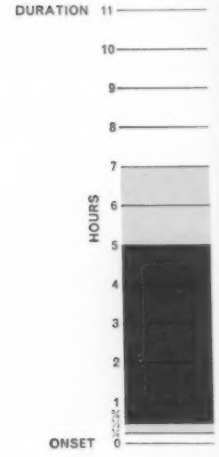

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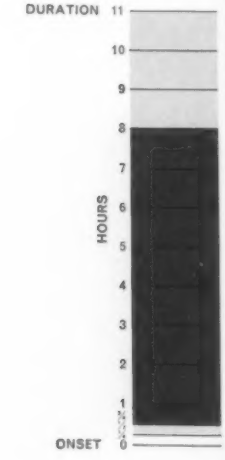

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